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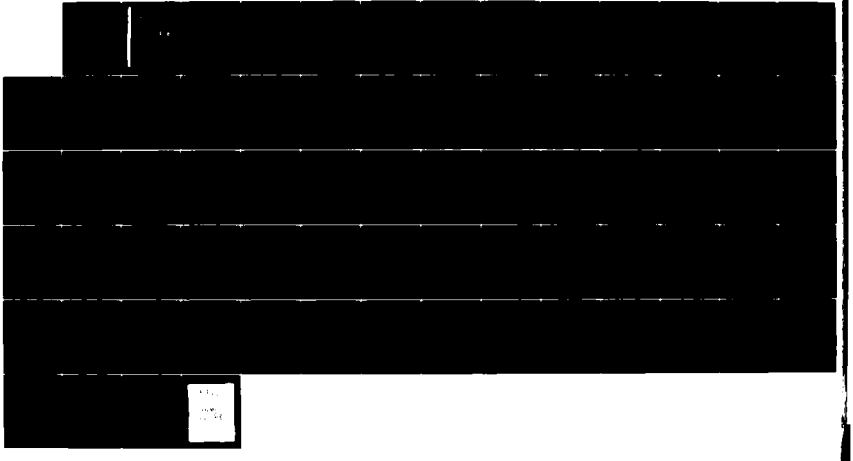

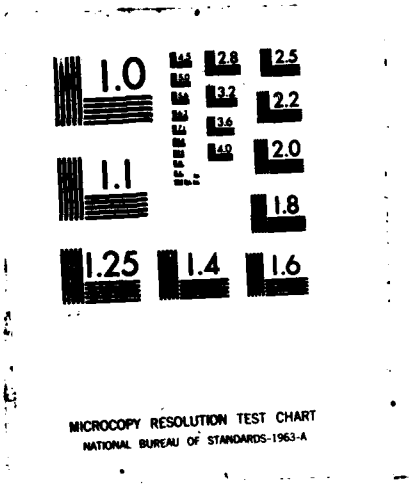
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MODELS OF CEREBRAL-BODY PERFUSION AND CEREBRAL CHEMICAL TRANSPORT

S.Sorek[1], J. Bear[2], and M. Feinsod[3]

in Collaboration with

K. Allen[4], L. Bunt[5] and S. Ben-Haim[6]

March 1988

SCIENTIFIC REPORT NO 3

Approved for public release, distribution unlimited.

Prepared for

The United States Air Force, Air Force Office of Scientific Research

and

The European Office of Aerospace Research and Development, London, England

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ABSTRACT

In this research, a sequence of models is constructed to simulate the movement of fluids and chemicals in the cerebrovascular system. One model simulates the nonsteady response of perfusion in various sections of the brain. In a second model, certain relevant parts of the body are added to form a single brain-body model. A third model simulates the transport of selected chemical components through the cerebrovascular system. Predictions derived from the brain model were shown to be well within the range of available clinical observations. The brain-body model describes the interaction between the cerebral, the cardiovascular and the respiration systems. It is excited by expiration/inspiration fluxes and accounts for the effects of hydrostatic, environmental pressures, flight maneuvers with excessive (head to bottom) gravitation acceleration and resuscitation procedures. In simulating chemical processes in the brain, the model accounts for CO_2, HCO_3^- and H^+, as they are transported by perfusion and diffusion in the presence of chemical reactions. This model also focuses on the flow control between brain arteries and capillaries, due to changes in CO_2 concentration.

NON-STEADY COMPARTMENTAL MODEL OF INTERACTIVE PERFUSION BETWEEN CEREBRAL AND BODY SYSTEMS

S. Sorek,[1] K. Allen,[2] M. Feinsod,[3] S. Ben Haim[4]
J. Bear[5] and L. Bunt[6]

ABSTRACT

A lumped parameter model is developed to simulate perfusive flux and pressure interaction between the cerebral and the body systems. Its objective is to study the dynamic interaction between the cranio-spinal, body respiratory and the heart systems that influence the brain, as well as the influence of conditions in the environment on the body. By providing forecasts of departures from a normal behavior, the model will serve the following medical purposes: (a) facilitate the understanding of the physiology and the mechanisms that preserve the delicate brain in the face of living stress, and (b) provide information for management in deviant cases.

The compartmental model consists of six compartments that describe the cerebral system, and eight compartments that are assigned to the body system. The model also accounts for the surrounding environment affecting the abdominal, inhale/exhale fluxes. Altitudes assigned to the compartments introduce the effect of hydrostatic pressure.

Key Words: Compartmental modelling, interaction between cerebral respiratory and heart systems; perfusion flux and pressure; conductances; compliances; environmental pressure; hydrostatic pressure; inhale/exhale fluxes.

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1. INTRODUCTION

In earlier papers (Karni et al. 1987; Sorek et al. 1987a, 1987b), a compartmental model was built to simulate the perfusion in the cerebrovascular system. The model provided information on pressures and fluxes in response to excitation in the form of temporal flux and pressure changes at the internal carotid artery. The influx to and efflux from the cerebrovascular system were introduced, respectively, as external conditions imposed on the internal carotid artery, and the jugular bulb.

In the present work, this model is extended to include both the cerebrovascular and the body system in a single model. The objective is to enable the study of the dynamic interaction between these two systems. In this model, relevant parts of the brain and of the human body are represented as compartments that interact with each other, e.g., in the form of pressure transmission and exchange of fluid. Each such compartment is represented by lumped, or averaged, properties and state variables of that organ. Examples of such lumped parameters are pressure in a compartment, influx/efflux through its boundaries and fluid source/sink terms.

The compartmental model is comprised of six compartments that represent the cerebral system and eight compartments assigned to the body system. The body portion of the compartmental design involves only those parts of the body that are relevant to the cerebral system, i.e., interact grossly with the latter. Accordingly, these parts include mainly the heart and the respiratory systems.

The model also accounts for the influence of the environment surrounding the body, e.g., atmospheric pressure, pressure at high and low altitudes, high underwater pressure, vacuum and excessive gravity acceleration, such as encountered in flight maneuvers. It also takes into consideration differences in elevation between compartments. This means that it takes into account hydrostatic pressure.

Excitations of the model are introduced through changes in inhale/exhale rates and environmental pressure changes exerted on the abdominal. Extreme intervention, such as resuscitation and/or clogging in the heart system, can be introduced via changes in the appropriate compartmental conductances and compliances.

The diagrammatic layout of the compartments is such as to assist a medical clinician in the interpretation of the model image of the human body, as when examining an X-ray plate. The model will guide clinicians by predicting the brain-body perfusion responses to various excitation, thus enhancing the physiological understanding, fault finding and consequent management in deviant cases of this complex system.

2. MODEL TOPOLOGY

The cerebral section of the model is based on the works of Karni et al. (1987) and Sorek et al. (1987), and is comprised of the following compartments (Fig. 1):

Arterial Cranium (A_C) - Consists of four supply vessels through the right and left internal carotid and vertebral arteries, with arteriolar branches.

Capillaries (C) - Represents the sult of brain capillaries, choroid plexus and arteriolar/venous capillaries.

Venous Cranium (V_C) - This is a 'lake' of blood confined by thin walls immersed in the brain mass. It contains a controlled mechanism to influence quick and slow fluid movement in the brain during stress. It comprises deep and superficial systems, normally freely anastomising.

Venous Sinuses (S) - These are encased in semi-rigid walls to prevent collapse in all but extreme conditions of compression.

The Cerebro-Spinal Fluid is contained in two compartments:

Ventricles (F_{IV}) - The four ventricles are treated as a true compartment with its own inflow and outflow. Although, normally, the resistance to the latter is low (as the aqueduct of Silvius depends on a pulsative drive to maintain its patency), in disease, high resistance and even occlusion may occur and isolate part of the ventricular system. In such cases, we introduce in the model the extra ventricular and the spinal fluid as an additional compartment.

Extra Ventricular CSF + Spinal Fluid (F_{EV}) - The cisterus sulci and spinal fluid compartment maintains a free communication with the CSF extra ventricular and, to a lesser extent, with the four main ventricles.

Compartments representing the extra-cranial venous (systemic) circulation are:

Extra-thecal venous plexus (V_{ET}) - A by-pass of the systemic flow included in the bony spinal portion of the cranial-spinal compartment. Normally, this compartment is much less involved in the circulation to the cerebral system. However, in special cases it communicates directly with the ventricles through the spinal and extra ventricular fluid. Therefore, we include it to accommodate abnormal situations.

Brain Tissue (B) - This compartment is placed diagrammatically as a central one, emphasizing its vulnerability, especially due to its location between the venous compartments. All pressures acting on B must be in such balance as to preserve the tissue physically, yet allow and promote optimal macro and micro circulation of fluid transporting metabolites.

The body section of the model is comprised of the following compartments:

Respiratory System (R) - This compartment is activated by the inhale/exhale flux. Its volume deforms through interaction with the heart system, abdominal, superior vena cava and body's arteries.

Abdominal (B_D) - This compartment is subject to volume changes initiated by the environment pressure, inferior vena cava and the respiratory system.

The heart system circulation receives an input perfusion from the superior vena cava and a feedback input from the inferior vena cava. The input flux is injected to the Right Ventricle (R_V) which mutually interacts, by volume deformation, with the respiratory system, and by flow with the Pulmonary (P). The pulmonary communicates by mutual volume deformation with the respiratory compartment and (by flow) with the Left Ventricle (L_V). The left ventricle exchanges volume deformations with the respiratory systems and discharges flow to the body arteries.

Body Arteries (A_B) - This compartment receives its inflow from the left heart ventricle and introduces the major inflow to the cerebral arteries. It interacts, via volume deformation, with the respiratory system, and discharges flow into the superior and inferior vena cava compartments.

Superior Vena Cava (V_{SC}) - This compartment receives the outflow from the cerebral system. It also receives inflow from the inferior vena cava and from body arteries and discharges it to

the right ventricle. Volume deformation interaction exists with the respiratory system.

Inferior Vena Cava (V_{IC}) - This compartment enables flow between body arteries and superior vena cava. It interacts by volume deformations with the abdominal, thus implicitly obtaining information from the environment which is then transmitted as back flow to the right ventricle.

Next we describe the resistances $R_{ij}\,(\equiv R_{ji})$ and compliances $C_{ij}\,(\equiv C_{ji})$, ascribed to the various compartments. Here, subscript ij in $(\ )_{ij}$ denotes the mutual boundary of compartments i and j.

$R_{A_cA_B}$ Carotid Body resistance that regulates and controls the inflow from the body to the cerebral arteries. The control is governed by the flux, Q_A, to the cerebral system.

C_{A_cB} Compliance between the brain tissue and cranial arteries compartments.

$C_{A_cF_{SV}}$ Compliance that attenuates the arterial pulse transmitted by large vessels traversing the basal, cisternal, sulcal spaces.

R_{A_cC} The sum of the cranial arteries, capillary and choroid plexus resistances. The resistance associated with the capillary is auto-regulatory control. This control between the arteriolar and capillary vessels, attenuates the systole artery pulse.

R_{CV_c} Resistance of the Arteriolar/Venous capillary, accounting for the pressure drop observed between them.

R_{CB} Resistance of the Blood-Brain barrier (between the capillary and the brain tissue).

$R_{CF_{IV}}$ Endothelial resistance of the Blood-CSF barrier. It describes the choroid plexus and ependynial secretion.

$C_{CF_{IV}}$ Compliance manifesting the arterial pulse transmitted to the ventricle CSF by the choroid plexus and the extra-cellular fluid.

R_{V_cB} Resistance representing the Blood-Brain barrier (involved in cerebral oedema).

R_{V_cS} A resistance comprised of two gates. First, the outlet from the deep venous circulation into the straight sinus via the great cerebral vein of Galen. According to Le Gros

Clark, an auto-regulatory control may be associated with this outflow.

The second component is the superior cortical veinous outflow into the sagittal sinus. An observable pressure drop exists across this resistance under normal conditions.

$R_{F_{IV}B}$ Ependumal resistance of the CSF-Brain barrier.

$C_{BF_{IV}}$ Multifrequency pulsed compliance, transmitted rhythmically by the brain to the ventricle for axial drive of CSF.

$R_{F_{IV}F_{EV}}$ Resistance that exists only in the case of strong stenosis, between the ventricles and the extra ventricular compartments.

$R_{F_{EV}S}$ Resistance manifesting villous tufts secretion into the venous sinus.

$C_{SF_{EV}}$ A low Compliance across the semi-rigid sinus walls.

$R_{F_{EV}V_{SC}}$ Resistance that manifests the slow secretion area around the spinal root sleeves.

$C_{F_{EV}V_{ET}}$ Compliance between the Intradural spinal fluid and the systemic venous flux, across the dura and the extra-thecal venous plexus. This mediates postural, respiratory, abdominal and other body fluctuations, while setting up the intra cranial pressure level.

$R_{V_{ET}V_{SC}}$ Resistance to secondary flow communication between the extra-thecal venous plexus and the superior vena cava.

$R_{V_{SC}A_B}$ Resistance to inflow from body arteries.

$C_{V_{SC}R}$ Compliance created by the respiratory venous flux. This compliance is controlled by the involuntary/voluntary variations in the respiratory rhythms.

$R_{V_{SC}R_V}$ Resistance between the superior vena cava and the heart system via the right ventricle

$R_{V_{SC}V_{IC}}$ Back flow resistance into the superior vena cava from the inferior one.

$C_{RR_V}, C_{RP}, C_{RL_V}$

These are the compliances between the respiratory and the heart system, comprised

of the right ventricle, pulmonary circulation and the left ventricle, respectively.

C_{RA_B} Compliance of the respiratory and body arteries.

C_{RB_D} Compliance between the respiratory and the abdominal. It transmits the environmental effects to the abdominal.

R_{R_VP} Inflow resistance from the right ventricle to the pulmonary section.

R_{PL_V} Circulatory resistance from the pulmonary to the the right ventricle.

$R_{L_VA_B}$ Resistance to flow discharged from the left ventricle (leaving the heart system) into the body arteries.

$R_{A_BV_{IC}}$ Back flow resistance, from the body arteries into the inferior vena cava, to become a flow feedback to the heart system.

$C_{B_DV_{IC}}$ Compliance between the abdominal and the inferior vena cava, transmitting the environmental effect to the abdominal.

C_{B_DA} Compliance due to direct communication between the surrounding environment and the abdominal.

Next, we write the perfusion equations for the entire cerebral-body compartmental setup.

3. FLOW EQUATIONS

Let us consider a single incompressible fluid phase that approximately represents all the relevant fluids in the brain-body system.

In writing the fluid flow, or balance,equations we consider mass and momentum balances for each compartment of the cerebral-body compartment system.

The model described here accounts for an infinite environmental (e.g., the surrounding atmosphere, or an experimental setup testing the influence of being subjected to several g's).

Essentially, each balance equation states that the temporal rate of increase of either the fluid mass, or its momentum in a compartment, is equal to the amount of net influx of that quantity

through the compartment's boundaries plus the external sources within the compartment. For a constant density fluid, the mass balance reduces to a volume balance.

The fluid's volume balance equation in compartment n takes the form

$$\frac{dV_n}{dt} + \sum_i q_{ni} = Q_n \tag{1}$$

where $V_n(t)$ denotes the volume of fluid in compartment n at time t (equal to the compartment's volume), Q_n is the source associated with compartment n, and q_{ni} denotes the flux flowing out of compartment n, through the boundary of the compartment, to its adjacent i compartment. This non rigidity of the compartment's boundaries (=walls) is expressed by a compliance factor, C_{nj}, defined by

$$C_{nj} = \frac{dV_n}{d(p_{nj})} \tag{2}$$

where $p_{nj} \equiv p_n - p_j$ denotes the pressure difference between compartments n and j, on both sides of their common wall.

For low Reynolds number flow, the momentum balance of a fluid moving through a capillary tube can be shown to reduce to an equation that expresses linear proportionality between flux and driving force. The latter is composed of a pressure gradient and a gravity term. Here we assume that a similar expression governs the flux between adjacent compartments. Hence

$$q_{ni} = Z_{ni}(p_{ni} + \gamma H_{ni}) = (zh)|_{ni} \tag{3}$$

where $(zh)|_{ni}$ $(\equiv z|_{ni} h|_{ni})$, Z_{ni} is the conductance associated with the flow wall between compartments n and i, H_{ni} $(\equiv H_n - H_i)$ is the altitude difference between compartments n and i, γ is the fluid's specific weight, h_{ni} $(= \frac{p_{ni}}{\gamma} + H_{ni})$ denotes the piezometric head difference between compartments n and i and z_{ni} $(= \gamma Z_{ni})$ is called the hydraulic conductivity factor between compartments n and i.

Upon substituting (2) and (3) into (1), we obtain

$$\sum_i (z\dot{h})|_{ni} + \sum_j (C\dot{p})|_{nj} = Q_n \tag{4}$$

where $\dot{p}_{nj} (\equiv \frac{d}{dt}(p_n - p_j) = \dot{p}_n - \dot{p}_j)$ denotes the temporal rate of increase in the difference in pressure between compartments n and its adjacent one, j.

Under certain abnormal conditions, a number of compartments become active. These are the extra ventricular and spinal fluid (F_{EV}) and extra-thecal venous plexus (V_{ET}). In the mathematical model, this fact is expressed by introducing a parameter λ_{mn} which can be set either to $\lambda_{nm} = 0$ for normal conditions, or to $\lambda_{nm} = 1$ for abnormal ones.

In view of (4), we write the following compartmental fluid balance equations:

$$A_C: \quad 0 = -(z\dot{h})|_{A_B A_C} + (z\dot{h})|_{A_C C} + (C\dot{p})|_{A_C B} + (\lambda C\dot{p})|_{A_C F_{EV}} \tag{5.1}$$

$$C: \quad 0 = -(z\dot{h})|_{A_C C} + (z\dot{h})|_{CB} + (z\dot{h})|_{CV_C} + (z\dot{h})|_{CF_{IV}} + (C\dot{p})|_{CF_{IV}} \tag{5.2}$$

$$V_C: \quad 0 = -(z\dot{h})|_{CV_C} - (z\dot{h})|_{BV_C} + (z\dot{h})|_{V_C S} + (C\dot{p})|_{V_C B} \tag{5.3}$$

$$B: \quad 0 = -(z\dot{h})|_{CB} - (z\dot{h})|_{F_{IV}B} + (z\dot{h})|_{BV_C} + (C\dot{p})|_{BV_C} + (C\dot{p})|_{BF_{IV}} + (C\dot{p})|_{BA_C} \tag{5.4}$$

$$S: \quad 0 = (z\dot{h})|_{SV_{SC}} - (z\dot{h})|_{V_C S} - (z\dot{h})|_{F_{EV}S} + (C\dot{p})|_{SF_{EV}} \tag{5.5}$$

$$F_{IV}: \quad 0 = -(z\dot{h})|_{CF_{IV}} + (z\dot{h})|_{F_{IV}B} + (\lambda z\dot{h})|_{F_{IV}F_{EV}} + (C\dot{p})|_{F_{IV}B} + (C\dot{p})|_{F_{IV}C} \tag{5.6}$$

$$\begin{aligned} F_{EV}: \quad 0 = {} & (z\dot{h})|_{F_{EV}S} + (\lambda z\dot{h})|_{F_{EV}V_{SC}} - (\lambda z\dot{h})|_{F_{IV}F_{EV}} + (C\dot{p})|_{F_{EV}S} + \\ & + (\lambda C\dot{p})|_{F_{EV}A_C} + (\lambda C\dot{p})|_{F_{EV}V_{ET}} \end{aligned} \tag{5.7}$$

$$V_{ET}: \quad 0 = (\lambda z\dot{h})|_{V_{ET}V_{SC}} + (\lambda C\dot{p})|_{V_{ET}F_{EV}} \tag{5.8}$$

$$\begin{aligned} V_{SC}: \quad 0 = {} & -(z\dot{h})|_{SV_{SC}} - (z\dot{h})|_{V_{IC}V_{SC}} - (z\dot{h})|_{A_B V_{SC}} + (z\dot{h})|_{V_{SC}R_V} - \\ & + (\lambda z\dot{h})|_{V_{ET}V_{SC}} - (\lambda z\dot{h})|_{F_{EV}V_{SC}} + (C\dot{p})|_{V_{sc}R} \end{aligned} \tag{5.9}$$

$$V_{IC}: \quad 0 = -(z\dot{h})|_{A_B V_{IC}} + (z\dot{h})|_{V_{IC}V_{SC}} + (C\dot{p})|_{V_{IC}B_D} \tag{5.10}$$

$$A_B:\ 0=(z\dot{h})|_{A_BA_C}-(z\dot{h})|_{L_VA_B}+(z\dot{h})|_{A_BV_{SC}}+(z\dot{h})|_{A_BV_{IC}}+(C\dot{p})|_{A_BR} \tag{5.11}$$

$$R_V:\ 0=-(z\dot{h})|_{V_{SC}R_V}+(z\dot{h})|_{R_VP}+(C\dot{p})|_{R_VR} \tag{5.12}$$

$$P:\ 0=-(z\dot{h})|_{R_VP}+(z\dot{h})|_{PL_V}+(C\dot{p})|_{PR} \tag{5.13}$$

$$L_V:\ 0=-(z\dot{h})|_{PL_V}+(z\dot{h})|_{L_VA_B}+(C\dot{p})|_{L_VR} \tag{5.14}$$

$$R:\ Q_R=(C\dot{p})|_{RV_{SC}}+(C\dot{p})|_{RR_V}+(C\dot{p})|_{RP}+(C\dot{p})|_{RL_V}+(C\dot{p})|_{RB_D}+(C\dot{p})|_{RA_B} \tag{5.15}$$

$$B_D:\ 0=(C\dot{p})|_{B_DR}+(C\dot{p})|_{B_DV_{IC}}+(C\dot{p})|_{B_DA}\ . \tag{5.16}$$

Since the environment is of infinite extent, we can write the relations

$$Q_R=C_{B_DA}\,\dot{p}_{B_D} \tag{6.1}$$

$$\dot{p}_A=0\ . \tag{6.2}$$

We assume a Monro-Kellie postulate according to which the (almost) rigidity of the skull dictates that

$$\int_T Q_S\,dt=\int_T Q_A\,dt \tag{7}$$

where T is the time period.

A stenosis in the passage between the F_{IV} and F_{EV} compartments, initiates a build-up of the compliance between the F_{EV} and A_C compartments. This, in return, indicates that

$$\lambda_{F_{IV}F_{EV}}=\lambda_{F_{EV}A_C}\equiv\lambda\ . \tag{8}$$

Under normal conditions, with free communication between F_{IV} and F_{EV} compartments ($\lambda_{F_{IV}F_{EV}}\equiv\lambda=0$), both the main ventricle and the extra ventricular will merge into one compartment (the F compartment), resulting in

$$h_{F_{IV}}=h_{F_{EV}}\equiv h_F\quad\text{with}\quad\lambda=0\ . \tag{9}$$

Note that in (9) we have assumed $H_{F_{IV}}=H_{F_{EV}}\equiv H_F$, because only minor differences exist

between their values.

Let us now combine all compartmental balance equations into a global matrix form. For the normal behavior (i.e. $\lambda_{n,m} = 0$), and in view of (5) and (9), we obtain

$$\underline{\underline{C}}\,\frac{d\underline{h}}{dt} + \underline{\underline{z}}\,\underline{h} = \underline{Q} \tag{10}$$

where

$$\frac{d\underline{h}}{dt} = \frac{d\underline{p}}{dt} \equiv \dot{\underline{p}} \qquad \left(\frac{d\underline{H}}{dt} = 0\right),$$

$$\underline{h} = [h_{A_C}, h_C, h_B, h_{V_C}, h_F, h_S, h_{V_{SC}}, h_{V_{IC}}, h_{A_S}, h_{R_V}, h_{L_V}, h_P]^T \tag{11.1}$$

$$\underline{Q} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \dfrac{C_{V_{SC}R}(C_{B_P} - C_{B_PR})}{\bar{C}}\,Q_R \\ \dfrac{C_{V_{SC}B_P}}{\bar{C}}\,(C_{B_PR} - C_R)\,Q_R \\ \dfrac{Q_R}{\bar{C}}\,[C_{A_PB_P}(C_{B_PR} - C_R) + C_{A_PR}(C_{B_P} - C_{B_PR})] \\ \dfrac{C_{R_VR}}{\bar{C}}\,(C_{B_P} - C_{B_PR})Q_R \\ \dfrac{C_{L_VR}}{\bar{C}}\,(C_{B_P} - C_{B_PR})Q_R \\ \dfrac{C_{PR}}{\bar{C}}\,(C_{B_P} - C_{B_PR})Q_R \end{bmatrix} \tag{11.2}$$

The non zero elements of the $\underline{\underline{z}}$ matrix are:

$$z_{1,1}=[z_{A_cC}+z_{A_aA_c}] \quad z_{1,2}=-z_{A_cC} \quad z_{1,9}=-z_{A_aA_c}$$

$$z_{2,1}=-z_{A_cC} \quad z_{2,2}=[z_{A_cC}+z_{CB}+z_{CV_c}+z_{CF}] \quad z_{2,3}=-z_{CB} \quad z_{2,4}=-z_{CV_c} \quad z_{2,5}=-z_{CF}$$

$$z_{3,2}=-z_{CB} \quad z_{3,3}=[z_{CB}+z_{FB}+z_{BV_c}] \quad z_{3,4}=-z_{BV_c} \quad z_{3,5}=-z_{FB}$$

$$z_{4,2}=-z_{CV_c} \quad z_{4,3}=-z_{BV_c} \quad z_{4,4}=[z_{CV_c}+z_{BV_c}+z_{V_cS}] \quad z_{4,6}=-z_{V_cS}$$

$$z_{5,2}=-z_{CF} \quad z_{5,3}=-z_{FB} \quad z_{5,5}=[z_{CF}+z_{FB}+z_{FS}] \quad z_{5,6}=-z_{FS} \qquad (11.3)$$

$$z_{6,4}=-z_{V_cS} \quad z_{6,5}=-z_{FS} \quad z_{6,6}=[z_{SV_{sc}}+z_{V_cS}+z_{FS}] \quad z_{6,7}=-z_{SV_{sc}}$$

$$z_{7,6}=-z_{SV_{sc}} \quad z_{7,7}=[z_{V_{sc}V_{sc}}+z_{A_aV_{sc}}+z_{SV_{sc}}] \quad z_{7,8}=-z_{V_{sc}V_{sc}} \quad z_{7,9}=-z_{A_aV_{sc}} \quad z_{7,10}=-z_{R_VV_{sc}}$$

$$z_{8,7}=-z_{V_{sc}V_{sc}} \quad z_{8,8}=[z_{A_aV_{sc}}+z_{V_{sc}V_{sc}}] \quad z_{8,9}=-z_{A_aV_{sc}}$$

$$z_{9,1}=-z_{A_aA_c} \quad z_{9,7}=-z_{A_aV_{sc}} \quad z_{9,8}=-z_{A_aV_{sc}} \quad z_{9,9}=[z_{A_aV_{sc}}+z_{A_aV_{sc}}+z_{L_VA_a}+z_{A_aA_c}] \quad z_{9,11}=-z_{L_VA_a}$$

$$z_{10,7}=-z_{V_{sc}R_V} \quad z_{10,10}=[z_{V_{sc}R_V}+z_{R_VP}] \quad z_{10,12}=-z_{R_VP}$$

$$z_{11,9}=-z_{L_VA_a} \quad z_{11,11}=[z_{PL_V}+z_{L_VA_a}] \quad z_{11,12}=-z_{PL_V}$$

$$z_{12,10}=-z_{R_VP} \quad z_{12,11}=-z_{PL_V} \quad z_{12,12}=[z_{R_VP}+z_{PL_V}]$$

The non zero elements of the $\underline{\underline{C}}$ matrix are:

$$C_{1,1}=C_{A_cB} \quad C_{1,3}=-C_{A_cB}$$

$$C_{2,1}=C_{CF} \quad C_{2,5}=-C_{CF}$$

$$C_{3,1}=-C_{A_cB} \quad C_{3,3}=[C_{BV_c}+C_{BF}+C_{A_cB}] \quad C_{3,4}=-C_{BV_c} \quad C_{3,5}=-C_{BF}$$

$$C_{4,3}=-C_{BV_c} \quad C_{4,4}=C_{BV_c}$$

$$C_{5,2}=-C_{CF} \qquad C_{5,3}=-C_{BF} \qquad C_{5,5}=[C_{BF}+C_{FS}+C_{CF}] \qquad C_{5,6}=-C_{FS}$$

$$C_{6,5}=-C_{FS} \qquad C_{6,6}=C_{FS}$$

$$C_{7,7}=C_{V_{sc}R}\left[1-\frac{C_{V_{sc}R}C_{B_B}}{\bar{C}}\right] \qquad C_{7,8}=-\frac{C_{V_{sc}R}C_{B_BR}C_{B_BV_{sc}}}{\bar{C}} \qquad C_{7,9}=-\frac{C_{V_{sc}R}(C_{B_B}C_{RA_s}+C_{B_BR}C_{B_BA_s})}{\bar{C}} \qquad C_{7,10}=-\frac{C_{V_{sc}R}C_{B_B}C_{RR_v}}{\bar{C}}$$

$$C_{7,11}=-\frac{C_{V_{sc}R}C_{B_B}C_{RL_v}}{\bar{C}} \qquad C_{7,12}=-\frac{C_{V_{sc}R}C_{B_B}C_{RP}}{\bar{C}}$$

$$C_{8,7}=-\frac{C_{V_{sc}B_B}C_{B_BR}C_{RV_{sc}}}{\bar{C}} \qquad C_{8,8}=C_{V_{sc}B_B}\left[1-\frac{C_{V_{sc}B_B}C_R}{\bar{C}}\right] \qquad C_{8,9}=-\frac{C_{V_{sc}B_B}(C_RC_{B_BA_s}+C_{B_BR}C_{RA_s})}{\bar{C}} \qquad C_{8,10}=-\frac{C_{V_{sc}B_B}C_{B_BR}C_{RR_v}}{\bar{C}}$$

$$C_{8,11}=-\frac{C_{V_{sc}B_B}C_{B_BR}C_{RL_v}}{\bar{C}} \qquad C_{8,12}=-\frac{C_{V_{sc}B_B}C_{B_BR}C_{RL_v}}{\bar{C}}$$

$$C_{9,7}=-\frac{C_{V_{sc}R}}{\bar{C}}(C_{A_sB_B}C_{B_BR}+C_{A_sR}C_{B_B}) \qquad C_{9,8}=-\frac{C_{V_{sc}B_B}}{\bar{C}}(C_{A_sB_B}C_R+C_{A_sR}C_{B_BR}) \qquad C_{9,9}=\left[C_{A_sB_B}+C_{A_sR}-\frac{C_RC_{A_sB_B}^2+2C_{A_sB_B}C_{B_BR}C_{A_sR}+C_{A_sR}^2C_{B_B}}{\bar{C}}\right] \qquad (11.$$

$$C_{9,10}=-\frac{C_{RR_v}}{\bar{C}}(C_{A_sB_B}C_{B_BR}+C_{A_sR}C_{B_B}) \qquad C_{9,11}=-\frac{C_{RL_v}}{\bar{C}}(C_{A_sB_B}C_{B_BR}+C_{A_sR}C_{B_B}) \qquad C_{9,12}=-\frac{C_{RP}}{\bar{C}}(C_{A_sB_B}C_{B_BR}+C_{A_sR}C_{B_B})$$

$$C_{10,7}=-\frac{C_{R_vR}C_{B_B}C_{RV_{sc}}}{\bar{C}} \qquad C_{10,8}=-\frac{C_{R_vR}C_{B_BR}C_{B_BV_{sc}}}{\bar{C}} \qquad C_{10,9}=-\frac{C_{R_vR}(C_{B_B}C_{RA_s}+C_{B_BR}C_{B_BA_s}}{\bar{C}} \qquad C_{10,10}=C_{R_vR}\left[1-\frac{C_{RR_v}C_{B_B}}{\bar{C}}\right]$$

$$C_{10,11}=-\frac{C_{R_vR}C_{B_B}C_{RL_v}}{\bar{C}} \qquad C_{10,12}=-\frac{C_{R_vR}C_{B_B}C_{RP}}{\bar{C}}$$

$$C_{11,7}=-\frac{C_{L_vR}C_{B_B}C_{RV_{sc}}}{\bar{C}} \qquad C_{11,8}=-\frac{C_{L_vR}C_{B_BR}C_{B_BV_{sc}}}{\bar{C}} \qquad C_{11,9}=-\frac{C_{L_vR}(C_{B_B}C_{RA_s}+C_{B_BR}C_{B_BA_s})}{\bar{C}} \qquad C_{11,10}=-\frac{C_{L_vR}C_{RR_v}C_{B_B}}{\bar{C}}$$

$$C_{11,11}=C_{L_vR}\left[1-\frac{C_{L_vR}C_{B_B}}{\bar{C}}\right] \qquad C_{11,12}=-\frac{C_{L_vR}C_{B_B}C_{RP}}{\bar{C}}$$

$$C_{12,7}=-\frac{C_{PR}C_{B_B}C_{RV_{sc}}}{\bar{C}} \qquad C_{12,8}=-\frac{C_{PR}C_{B_BR}C_{B_BV_{sc}}}{\bar{C}} \qquad C_{12,9}=-\frac{C_{PR}(C_{B_B}C_{RA_s}+C_{B_BR}C_{B_BA_s})}{\bar{C}} \qquad C_{12,10}=-\frac{C_{PR}C_{B_B}C_{RR_v}}{\bar{C}}$$

$$C_{12,11}=-\frac{C_{PR}C_{B_B}C_{RL_v}}{\bar{C}} \qquad C_{12,12}=C_{PR}\left[1-\frac{C_{RP}C_{B_B}}{\bar{C}}\right]$$

Also,

$$C_{B_D} \equiv C_{B_D R} + C_{B_D V_{IC}} + C_{B_D A_B} \tag{11.5}$$

$$C_R \equiv C_{RV_{SC}} + C_{RP_V} + C_{RP} + C_{RL_V} + C_{RB_D} + C_{RA_B} \tag{11.6}$$

$$\bar{C} = C_{B_D} C_R - C_{B_D R}^2 \ . \tag{11.7}$$

Equation (10) is to be solved for the unknown $\underline{\dot{h}}$ vector, subject to an initial condition of the form

$$\underline{h}_{(t=0)} = \underline{h}_o \ . \tag{12}$$

Upon solving (10), together with (12), we obtain the solution for the temporal rates of change in piezometric head, $\dot{h}_{B_D}$ and $\dot{h}_R$, in the forms

$$\dot{h}_{B_D} = \frac{1}{\bar{C}} [(C_{B_D R} - C_R) Q_R + (C_R C_{B_D A_B} + C_{B_D R} C_{RA_B}) \dot{h}_{A_B} + C_R C_{B_D V_{IC}} \dot{h}_{V_{IC}} + \\ + C_{B_D R} C_{RV_{SC}} \dot{h}_{V_{SC}} + C_{B_D R} C_{RR_V} \dot{h}_{R_V} + C_{B_D R} C_{RP} \dot{h}_P + C_{B_D} C_{RL_V} \dot{h}_{L_V}] \tag{13}$$

$$\dot{h}_R = \frac{1}{\bar{C}} [(C_{B_D} - C_{B_D R}) Q_R + (C_{B_D} C_{RA_B} + C_{B_D R} C_{B_D A_B}) \dot{h}_{A_B} + C_{B_D R} C_{B_D V_{IC}} \dot{h}_{V_{IC}} + \\ C_{B_D} C_{RV_{SC}} \dot{h}_{V_{SC}} + C_{B_D} C_{RR_V} \dot{h}_{R_V} + C_{B_D} C_{RP} \dot{h}_P + C_{B_D} C_{RL_V} \dot{h}_{L_V}] \ . \tag{14}$$

The compartmental balance equation, written in the global compact form (10), involves conductivities and compliances expressed by the matrices $\underline{\underline{z}}$ and $\underline{\underline{C}}$, respectively. In order to solve for the piezometric head vector, $\underline{h}$, we need to know the $\underline{\underline{z}}$ and $\underline{\underline{C}}$ values. We shall, next, discuss an inverse method for estimating these parameters.

4. PARAMETER ESTIMATION

To predict the pressure and flux response of the model to external changes, the values of the parameters $\underline{\underline{C}}$ and $\underline{\underline{z}}$ must be known. In order to estimate them, we need measured values of pressure in the various compartments at a sufficient number of points in time. Typical phasic

pressures are depicted in Figs. 2-11.

In the present work, we assume that all conductivities and compliances have the form of a time step function i.e., they change from one constant value to another constant value, due to abnormal situations such as disease. Because $\underline{\underline{C}}$ and $\underline{\underline{z}}$ are constant during long time intervals, and $\underline{h}(t)$ is assumed cyclic, by taking a temporal average of (10), i.e., integration over a period of time divided by the period, we obtain

$$\underline{\underline{z}}\,\underline{h}^{*} = \underline{Q}^{*} \tag{15}$$

where h^* and Q^* denote mean values of the piezometric head and of the source term, respectively. Since $\underline{h}^{*}$ and $\underline{Q}^{*}$ are known averaged values, in order to solve for $\underline{\underline{z}}$ values, we rewrite (15) in the form

$$\underline{\underline{\Gamma}}^{*}\underline{z}^{V} = \underline{Q}^{*} \tag{16}$$

where (Γ) denotes the head difference between two communicating compartments.

In the cerebral portion of the model, we face ten conductivities against six balance equations. However, by virtue of the Monro-Kellie doctrine which assumes absolute rigidity of the cranial vault, actually only five equations of the six are independent. Thus for this redundancy, five additional conditions are needed. One of them is the mean influx to the CSF (F) compartment $Q_F^{*} = 0.3$ml/m.n. (Cutalar, 1968). Two more conditions are stipulated by physiological data. These conditions determine the scalar coefficients (Sorek et al. 1987) α and β defined as

$$\alpha = \frac{z_{V_c S}}{z_{FB}} \qquad (\alpha > 0) \tag{17}$$

and

$$\beta = \frac{z_{CB}}{z_{FB}} \qquad (0 \le \beta < \infty) \tag{18}$$

where α (= 10000) indicates the ratio of the vein-venous sinous to the cerebrospinal fluid-brain barrier, and $\beta(= 10^{-3})$ is the ratio of the blood-brain barrier to the cerebrospinal fluid-brain barrier.

The mean arterial influx, Q_A, which according to (3) equals the mean venous sinous efflux, is given by

$$Q_A^* = Q_S^* \equiv Q^* = 750\text{ml./min.}$$

Because Q_F^*, Q_A^* and Q_S^* are a-priori known, and the mean head values $h_{A_C C}^*$, h_{CF}^*, $h_{A_B A_C}^*$ and $h_{SV_{SC}}^*$ are also known, the following conductivities are immediately obtained.

$$z_{A_C A_B} = \frac{Q^*}{h_{A_B A_C}^*} \qquad z_{A_C C} = \frac{Q^*}{h_{A_C C}^*} \tag{19.1}$$

$$z_{GF} = \frac{Q_F^*}{h_{CF}^*} \qquad z_{SV_{SC}} = \frac{Q^*}{h_{SV_{SC}}^*} \; . \tag{19.2}$$

Also, for the given configuration of the heart system (Fig. 1), knowing the mean flux through any of the conductances, e.g. $Q_L^* = 5900\text{ml./min}$ through the boundary between compartments L_V and A_B, will yield

$$z_{L_V A_B} = \frac{Q_L^*}{h_{L_V A_B}^*} \qquad z_{PL_V} = \frac{Q_L^*}{h_{PL_V}^*} \tag{20.1}$$

$$z_{R_V P} = \frac{Q_L^*}{h_{R_V P}^*} \qquad z_{V_{SC} R_V} = \frac{Q_L^*}{h_{V_{SC} R_V}^*} \; . \tag{20.2}$$

We assume that the mean influx to the inferior vena cava compartment is a fraction, δ ($0 < \delta \leq 1$), of the efflux Q_L^* from the left heart ventricle. Therefore, we obtain

$$z_{V_{IC} V_{SC}} = \frac{\delta Q_L^*}{h_{V_{IC} V_{SC}}^*} \tag{20.3}$$

$$z_{A_B V_{IC}} = \frac{\delta Q_L^*}{h_{A_B V_{IC}}^*} \tag{20.4}$$

$$z_{A_B V_{BC}} = \frac{(1-\delta)Q_L^* - Q^*}{h^*_{A_B V_B C}} \quad . \tag{20.5}$$

Hence, in view of (17) to (20), equation (16) is constructed of the following matrix and vectors

$$\underline{\underline{\tilde{h}}}^* = \begin{bmatrix} h^*_{B_F} - \beta h^*_{CB} & 0 & 0 & h^*_{BV_C} \\ \beta h^*_{CB} & h^*_{CV_C} & 0 & 0 \\ h^*_{FB} & 0 & h^*_{FS} & 0 \\ \alpha h^*_{V_C S} & -h^*_{CV_C} & 0 & -h^*_{BV} \end{bmatrix} \tag{21.1}$$

$$\underline{z}^V = [z_{FB}, z_{CV_C}, z_{FS}, z_{BV_C}]^T \tag{21.2}$$

$$\underline{Q}^* = [0, Q^* - Q_F^*, Q_F^*, 0]^T \tag{21.3}$$

Upon solving the inverse problem for the conductivities, we move to the estimation of the compliances.

Given information of the simultaneous pulse wave recordings, $p_{(t)}$, and $\dot{p}_{(t)}$, in the different compartments and at various times $t^k, k = 1,2,\ldots,K$, equation (10) (or (5) and (6)) now yields a set of k relations for the compliances, for times t^k

$$\underline{\underline{\dot{\tilde{h}}}}^k \underline{C}^V = \underline{R}^k \tag{22}$$

where $\dot{(\ )} \equiv \frac{d}{dt}(\ )$.

$$\dot{\underline{\underline{h}}}^{k} = \begin{bmatrix} \dot{h}_{A_C B} & & & & & & & & & & \\ & \dot{h}_{CF} & & & & & & & & & \\ & & \dot{h}_{V_C B} & & & & & & & & \\ & & & \dot{h}_{SF} & & & & & & & \\ & & & & \dot{h}_{FB} & & & & & & \\ & & & & & \dot{h}_{V_{BC}R} & & & & & \\ & & & & & & \dot{h}_{V_{BC}B_D} & & & & \\ & & & & & & & \dot{h}_{R_V R} & & & \\ & & & & & & & & \dot{h}_{PR} & & \\ & & & & & & & & & \dot{h}_{L_V R} & \\ & & & & & & & & & & \dot{h}_{A_B R} \\ & & & & & & & & & & & \dot{h}_{RB_D} \end{bmatrix} \tag{23.1}$$

$$\underline{C}^{V} = [\, C_{A_C B}, C_{CF}, C_{V_C B}, C_{SF}, C_{BF}, C_{V_{BC}R}, C_{V_{BC}B_D}, C_{R_V R}, \\ , C_{PR}, C_{L_V R}, c_{A_B R}, C_{B_D R} \,]^{T} \tag{23.2}$$

$$\underline{R}^k = \begin{bmatrix} (zh)^k|_{A_B A_C} - (zh^k)|_{A_C C} \\ (zh^k)|_{A_C C} - (zh^k)|_{CB} - (zh^k)|_{CV_C} - (zh^k)|_{CF} \\ (zh^k)|_{CV_C} + (zh^k)|_{BV_C} - zh^k|_{V_{CB}} \\ (zh^k)|_{V_C S} + (zh^k)|_{FS} - (zh^k)|_{SV_S} \\ (zh^k)|_{V_C S} - (zh^k)|_{FB} - (zh^k)|_{SV_{SC}} + (zh^k)|_{A_C C} - (zh^k)|_{CB} - (zh^k)|_{CV_C} \\ (zh^k)|_{SV_{SC}} + (zh^k)|_{V_{IC} V_{SC}} + (zh^k)|_{A_B V_{SC}} - (zh^k)|_{V_{SC} R_V} \\ (zh^k)|_{A_B V_{IC}} - (zh^k)|_{V_{IC} V_{SC}} \\ (zh^k)|_{V_{SC} R_V} - (zh^k)|_{R_V P} \\ (zh^k)|_{R_V P} - (zh^k)|_{PL_V} \\ (zh^k)|_{PL_V} - (zh^k)|_{L_V A_B} \\ -(zh^k)|_{A_B V_{IC}} - (zh^k)|_{A_B V_{SC}} - (zh^k)|_{A_B A_C} + (zh^k)|_{L_V A_B} \\ -Q_R^k + (zh^k)|_{A_B V_{IC}} - (zh^k)|_{V_{IC} V_{SC}} \end{bmatrix} \quad (23.3)$$

Note that the z values in (23.3) are already known.

By the Gauss-Markov theorem, the $\underline{C}^V$ values are derived as an assortment of the set of informations through all K time observations (Sorek et al. 1987b), namely

$$\underline{C}^V = (\underline{\pi}^T \underline{\pi})^{-1} \underline{\pi}^T \underline{B} \quad (24)$$

where,

$$\underline{\pi} = \begin{bmatrix} \dot{\underline{h}}^1 \\ \hline \dot{\underline{h}}^2 \\ \hline . \\ . \\ . \\ \dot{\underline{h}}^K \end{bmatrix}_{K*13} \quad (25.1)$$

$$\underline{B} = [\underline{R}^1, \underline{R}^2, \ldots \underline{R}^K]^T_{1*K} \quad (25.2)$$

Since the $\underline{\underline{\dot{h}}}^k$ submatrices of π are main diagonalized, we can evaluate the $\underline{C}$ values directly.

$$C_{A_CB} = \frac{\sum_{k=1}^{K} \dot{h}^k_{A_CB}[(zh^k)|_{A_BA_C} - (zh^k)|_{A_CC}]}{\sum_{k=1}^{K} (\dot{h}^k_{A_CB})^2} \tag{26.1}$$

$$C_{CF} = \frac{\sum_{k=1}^{K} \dot{h}^k_{CF}[(zh^k)|_{A_CC} - (zh^k)|_{CB} - (zh^k)|_{CV_C} - (zh^k)|_{CF}]}{\sum_{k=1}^{K} (\dot{h}^k_{CF})^2} \tag{26.2}$$

$$C_{V_CB} = \frac{\sum_{k=1}^{K} \dot{h}^k_{V_CB}[(zh^k)|_{CV_C} + (zh^k)|_{BV_C} - (zh^k)|_{V_CS}]}{\sum_{k=1}^{K} (\dot{h}^k_{V_CB})^2} \tag{26.3}$$

$$C_{SF} = \frac{\sum_{k=1}^{K} \dot{h}^k_{SF}[(zh^k)|_{V_{CS}} + (zh^k)|_{FS} - (zh^k)|_{SV_S}]}{\sum_{k=1}^{K} (\dot{h}^k_{SF})^2} \tag{26.4}$$

$$C_{BF} = \frac{\sum_{k=1}^{K} \dot{h}^k_{FB}[(zh^k)|_{V_CS} - (zh^k)|_{FB} - (zh^k)|_{SV_{SC}} + (zh^k)|_{A_CC} - (zh^k)|_{CB} - (zh^k)|_{CV_C}]}{\sum_{k=1}^{K} (\dot{h}^k_{FB})^2} \tag{26.5}$$

$$C_{V_{SC}R} = \frac{\sum_{k=1}^{K} \dot{h}^k_{V_{SC}R}[(zh^k)|_{SV_{SC}} + (zh^k)|_{V_{IC}V_{SC}} + (zh^k)|_{A_BV_{SC}} - (zh^k)|_{V_{SC}R_V}]}{\sum_{k=1}^{K} (\dot{h}^k_{V_{SC}R})^2} \tag{26.6}$$

$$C_{V_{IC}B_D} = \frac{\sum_{k=1}^{K} \dot{h}^k_{V_{IC}B_D}[(zh^k)|_{A_BV_{IC}} - (zh^k)|_{V_{IC}V_{SC}}]}{\sum_{k=1}^{K} (\dot{h}^k_{V_{IC}B_D})^2} \tag{26.7}$$

$$C_{R_VR} = \frac{\sum_{k=1}^{K} \dot{h}^k_{R_VR}[(zh^k)|_{V_{SC}R_V} - (zh^k)|_{R_VP}]}{\sum_{k=1}^{K} (\dot{h}^k_{R_VR})^2} \tag{26.8}$$

$$C_{P_R} = \frac{\sum_{k=1}^{K} \dot{h}^k_{PR}[(zh^k)|_{R_VP} - (zh^k)|_{PL_V}]}{\sum_{k=1}^{K} (\dot{h}^k_{PR})^2} \tag{26.9}$$

$$C_{L_VR} = \frac{\sum_{k=1}^{K} \dot{h}^k_{L_VR}[(zh^k)|_{PL_V} - (zh^k)|_{L_VA_B}]}{\sum_{k=1}^{K} (\dot{h}^k_{L_VR})^2} \tag{26.10}$$

$$C_{A_BR} = \frac{\sum_{k=1}^{K} \dot{h}^k_{A_BR}[(zh^k)|_{L_VA_B} - (zh^k)|_{A_BA_C} - (zh^k)|_{A_BV_{SC}} - (zh^k)|_{A_BV_{IC}}]}{\sum_{k=1}^{K} (\dot{h}^k_{A_BR})^2} \tag{26.11}$$

$$C_{B_DR} = \frac{\sum_{k=1}^{K} \dot{h}^k_{RB_D}[-Q^k_R + (zh^k)|_{A_BV_{IC}} - (zh^k)|_{V_{IC}V_{SC}}]}{\sum_{k=1}^{K} (\dot{h}^k_{RB_D})^2} \tag{26.12}$$

Thus, we have completed writing the numerical algorithms for estimating the $\underline{z}$ and $\underline{C}$ values. The mean and temporal values of the fluxes, pressure and pressure rates are derived from phasic changes as depicted in Figs. 2-11.

Note that for the body system, the compartmental pressure and temporal rate of pressure change ride on the appropriate respiratory wave. However, for the cerebral system, this effect is

attenuated.

We assume a respiratory pressure wave of the form

$$p_R = 10 \sin \omega_R t \tag{27}$$

where $\omega_R = \frac{2\pi}{T_R}$ is the inspiration/respiration frequency, and T_R (= 3.4sec.) is taken as the respiratory cycle time.

We use the following altitude values:

H_{B_D} = 110 cm. $H_{V_{SC}}$ = 140 cm. H_{V_C} = 163 cm.
H_R = 135 cm. $H_{V_{IC}}$ = 126 cm. H_B = 163 cm.
H_{R_V} = 130 cm. H_{A_B} = 116 cm. H_F = 163 cm.
H_P = 130 cm. H_{A_C} = 160 cm. H_S = 163 cm.
H_{L_V} = 130 cm. H_C = 163 cm.

corresponding to a standing position. Also, we choose the following values for pressure and rates of pressure changes:

$$p_C = 30mm.Hg. \;;\; \dot{p}_C = 0$$
$$p_S = 2mm.Hg. \;;\; \dot{p}_s = 0$$
$$p_{V_{IC}} = 5mm.Hg. \;;\; \dot{p}_{V_{IC}} = 0 \;.$$

This concludes the calibration scheme for the brain-body compartmental model, with conductivities and compliances that remain constant during long time intervals.

5. PRESSURE WAVES

Once the linear model described by (10) has been calibrated, it is possible to obtain solutions for the pressure waves in all brain-body compartments. In incremental form, the solution of the differential matrix equation (10) for $\underline{h}$ is

$$\underline{h}_{(t+\Delta t)} = \exp(-\tau)[\underline{h}_{(t)} - \underline{\underline{z}}^{-1}\underline{Q}_{(t)}] + \underline{\underline{z}}^{-1}\underline{Q}(t) \;. \tag{28}$$

Here, $\Delta t\ (=t^{m+1}-t^{m})$ denotes a time difference between the frontier time level, t^{m+1}, and the backtime, t^{m}. The matrix τ reads

$$\tau = \Delta t\ \underline{\underline{C}}^{-1}\underline{\underline{z}} \tag{29}$$

The rational expansion of $\exp(-\tau)$, leads to the following formula

$$\exp(-\tau) \equiv \frac{\underline{\underline{I}}-(1-\theta)\tau}{\underline{\underline{I}}+\theta\tau} \quad (0 \le \theta \le 1) \tag{30}$$

in which $\underline{\underline{I}}$ is the unit matrix. Substituting (29) and (30) into (28), yields

$$\underline{h}_{(t+\Delta t)} = (\underline{\underline{I}}+\theta\tau)^{-1}[\underline{\underline{I}}-(1-\theta)\tau][\underline{h}_{(t)}-\underline{\underline{z}}^{-1}\underline{Q}_{(t)}] + \underline{\underline{z}}^{-1}\underline{Q}^{(t)}\ . \tag{31}$$

The coefficient θ controls the type of numerical solution scheme evolving in time. When $\theta = 0$, we have an explicit scheme $\theta = 1$, an implicit scheme, and $0 < \theta < 1$ is the mixed scheme case.

Thus, with the choice of θ, the head waves in the various compartments are calculated according to (10). In view of (3) and (31), we can also evaluate the compartmental pressures

$$\underline{P}_{(t+\Delta t)} = \{(\underline{\underline{I}}+\theta\tau)^{-1}[\underline{\underline{I}}-(1-\theta)\tau][\underline{h}_{(t)}-\underline{\underline{z}}^{-1}\underline{Q}_{(t)}] + \underline{\underline{z}}^{-1}\underline{Q}_{(t)}-\underline{H}\}\gamma \tag{32}$$

This completes the modelling of the brain-body perfusion pressure, as excited by environmental pressure and due to inspiration/expiration flux.

6. CONCLUSION

A compartmental model for perfusion pressure interplay between the cerebral, respiratory and heart systems is presented. The perfusion pressure response is initiated by compartments altitude, environmental pressure and inspiration/expiration flux.

Flow between compartments is governed by compartmental step function related conductivities and compliances that take the forms of time step functions.

The developed model can be used to guide the neurosurgeon in the interpretation of possible consequences of management methods applied to abnormal cases. Following are some

examples of management maneuvers that can be interpreted by numerical experiments of the model.

(a) Correction of a fault if recognizable and accessible, e.g., tumours, blockage of flow channels. This is the ideal case.

(b) Offsetting of destructive tensions that, usually, would be short term amending, e.g., reducing excess pressure usually done by shunting the CSF volume.

(c) Correcting mechanisms that fail to confine or maintain the system in optimal compliance against repeated stress in the long time, e.g., introducing a gas bubble in a sac into the large hydrocephalic ventricle in order to hold down the pressure peaks and create better Pressure-Volume-Time relationship.

In practice, the management of (b) is on the CSF bulk, where as for (c) it also involves the blood volume as an indirect means of promoting optimum flux.

The model can provide information for fault-finding, target identification and monitoring the results of rational management.

ACKNOWLEDGEMENT

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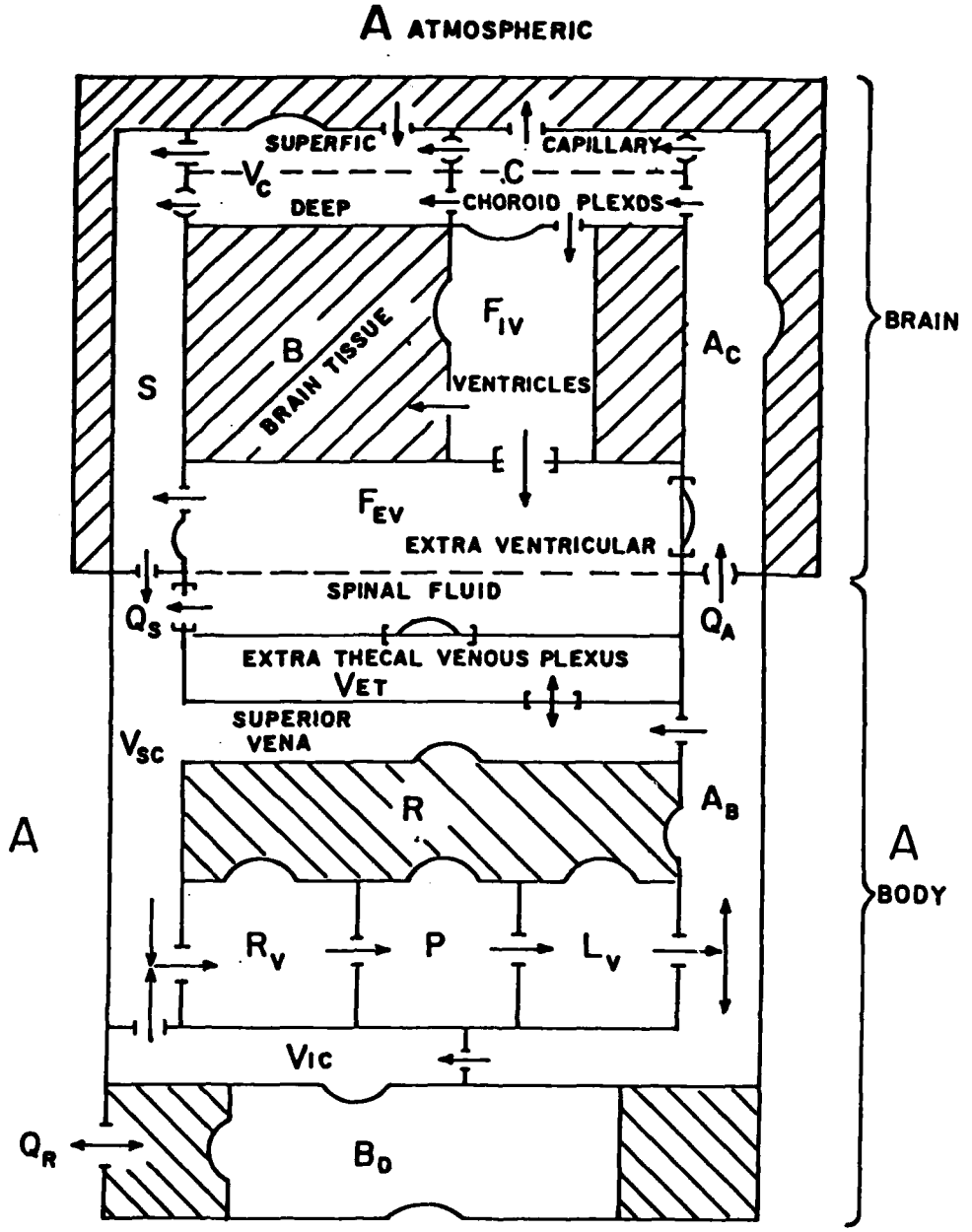

Figure 1: Cerebral – Body compartmental design.

⏚ – conductance; ~ – compliance.

⏚ – auto regulatory conductance; ‡ – element invoct in special situation

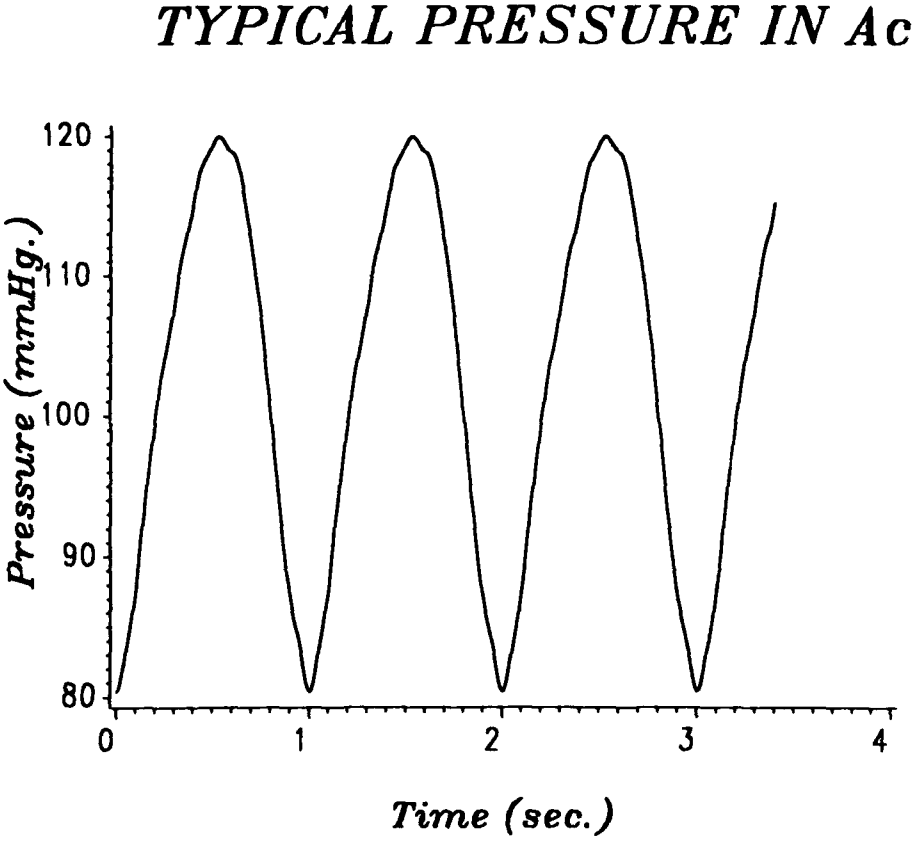

Figure 2: During one cycle of breathing (after Hamit et al.)

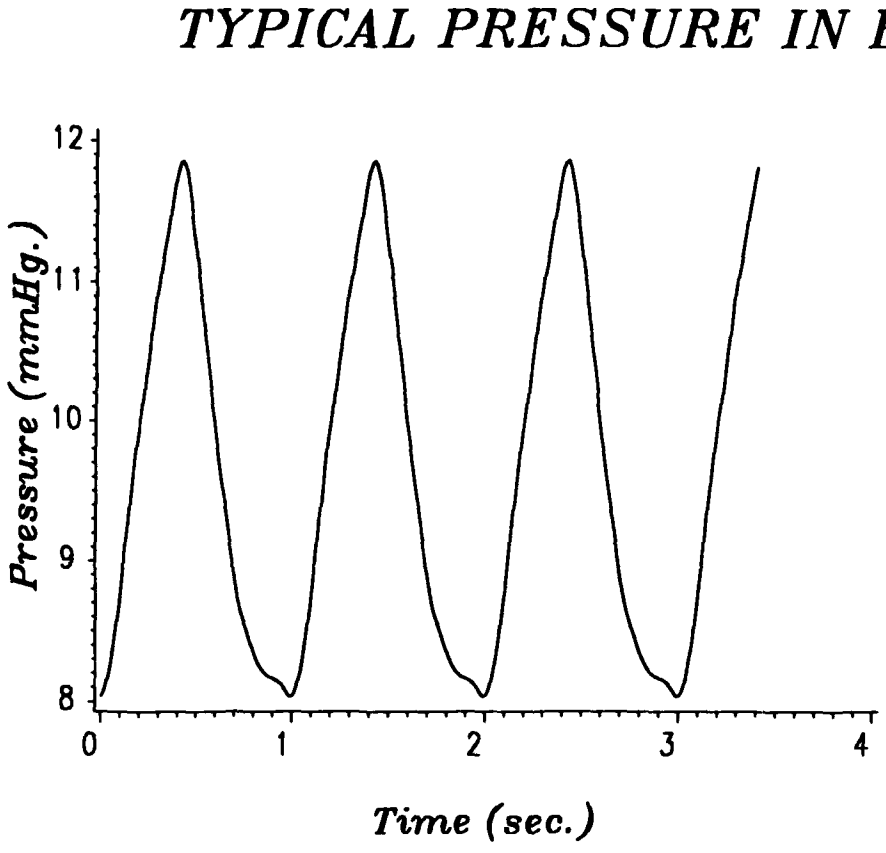

Figure 3: During one cycle of breathing (after Hamit et al.)

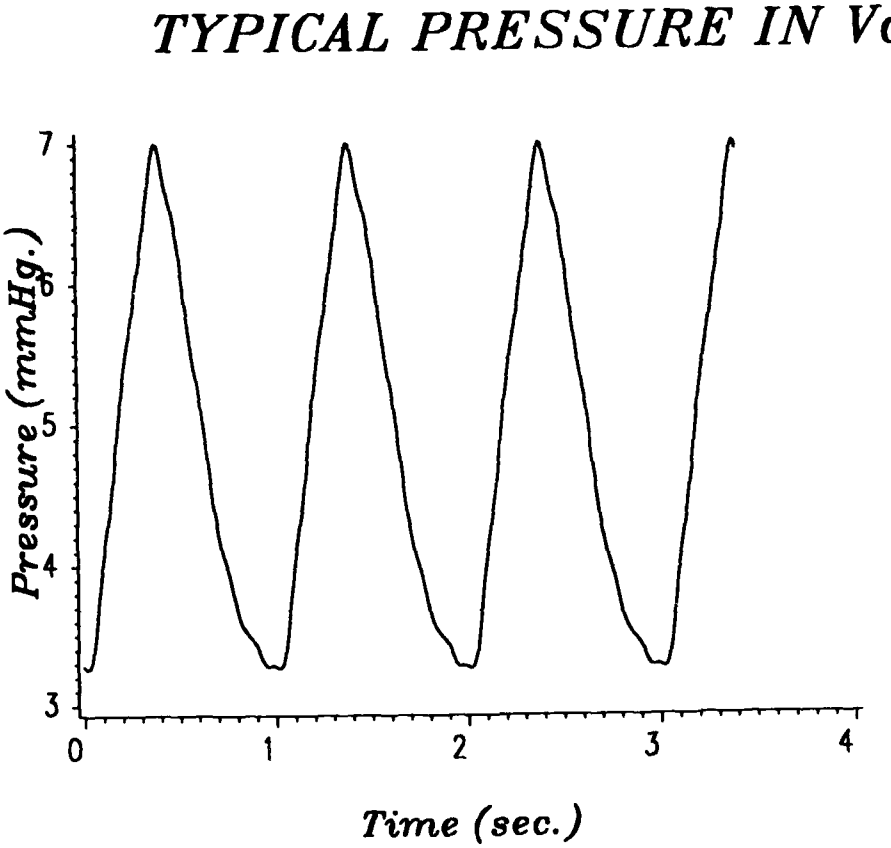

Figure 4: During one cycle of breathing (after Hamit et al.)

TYPICAL PRESSURE IN F

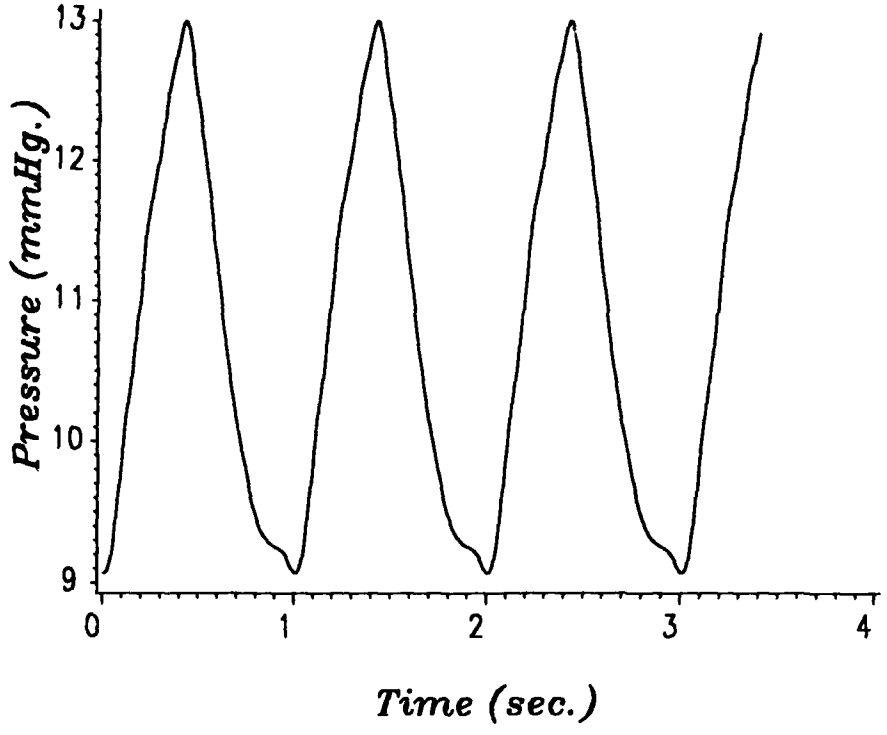

Figure 5: During one cycle of breathing (after Hamit et al.)

TYPICAL PRESSURE IN Ab

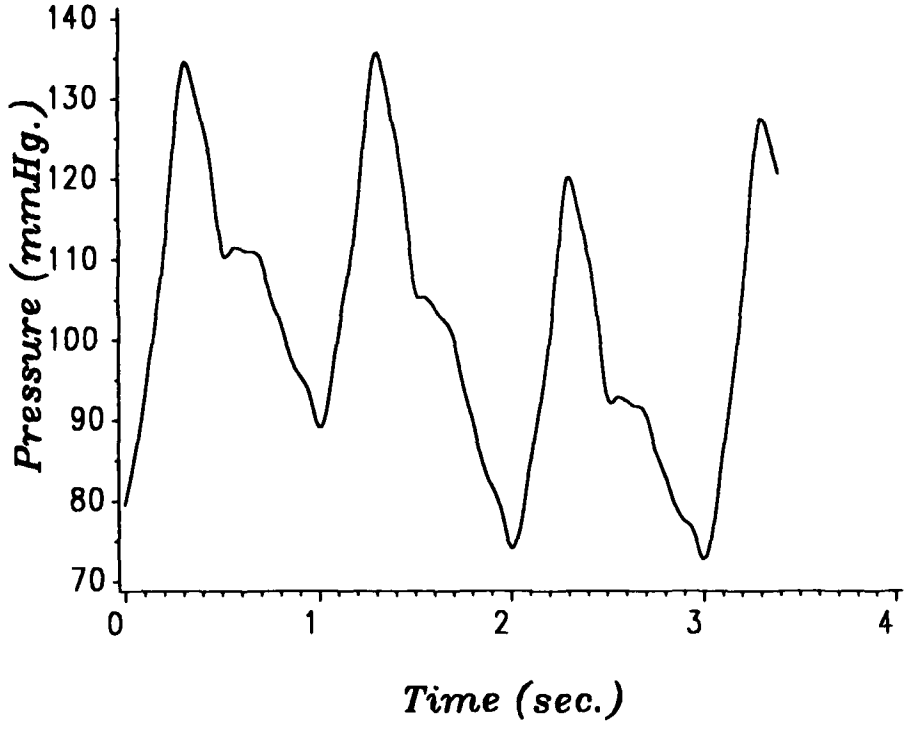

Figure 6: During one cycle of breathing (after Shepherd et al.)

TYPICAL PRESSURE IN Lυ

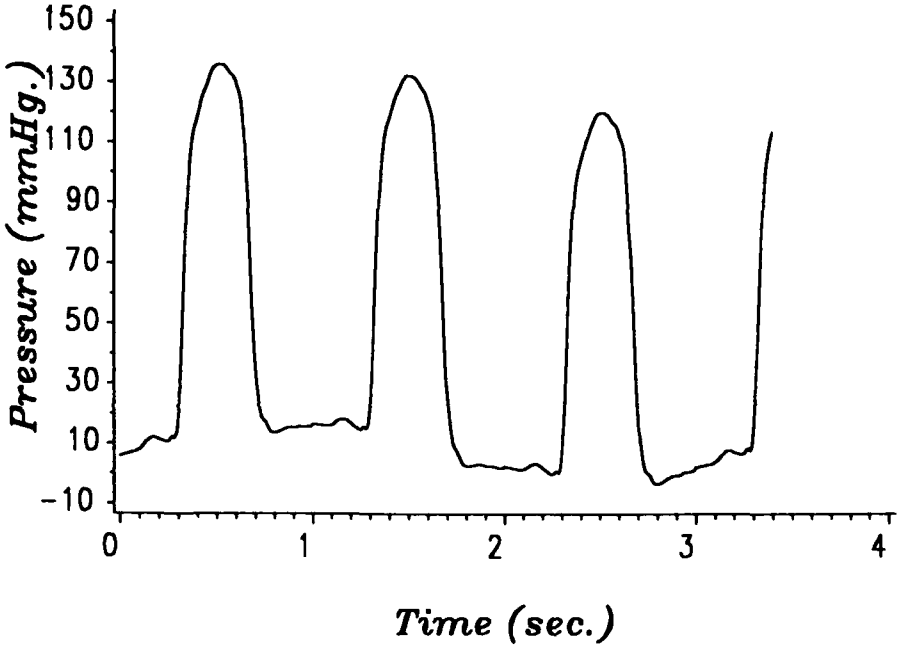

Figure 7: During one cycle of breathing (after Wiggers)

TYPICAL PRESSURE IN Rv

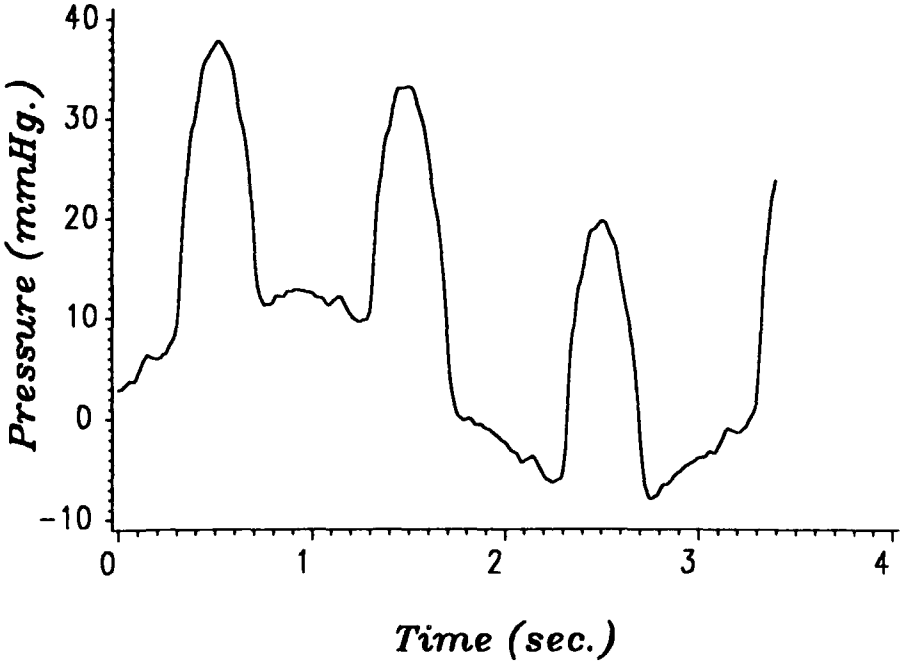

Figure 8: During one cycle of breathing (after Vernon et al.)

TYPICAL PRESSURE IN P

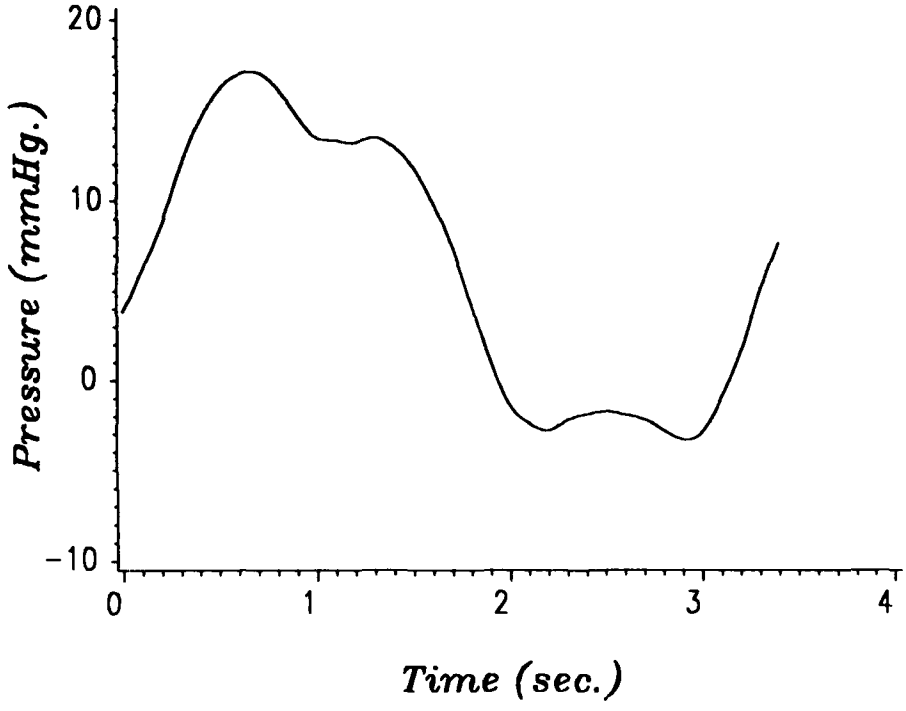

Figure 9: During one cycle of breathing (after Shepherd et al.)

TYPICAL Inspiration/Expiration FLUX

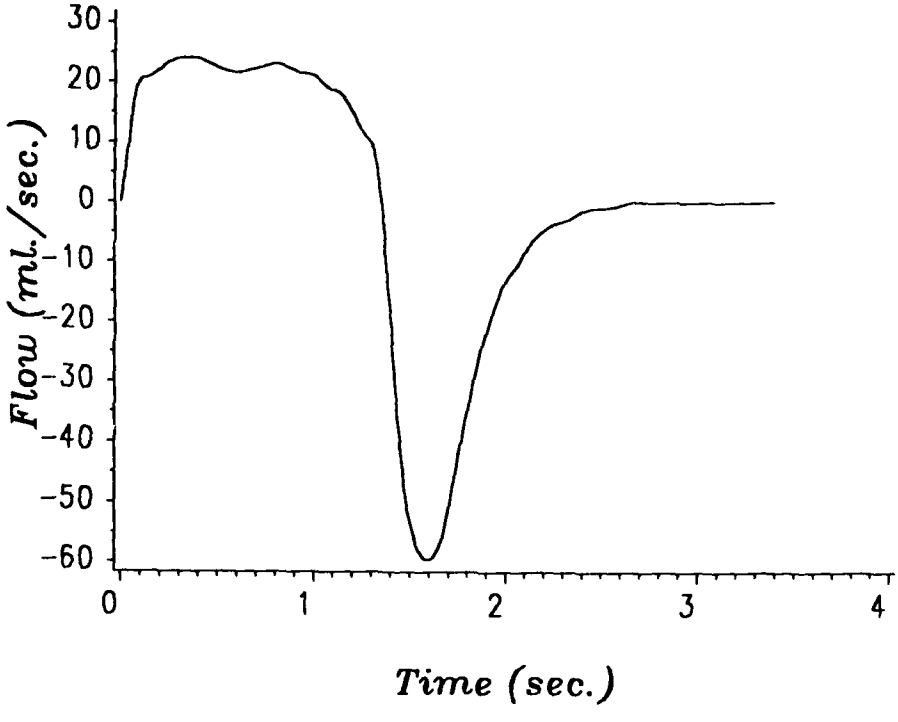

Figure 10: During one cycle of breathing (after Ben Haim et al.)

TYPICAL AORTIC FLOW

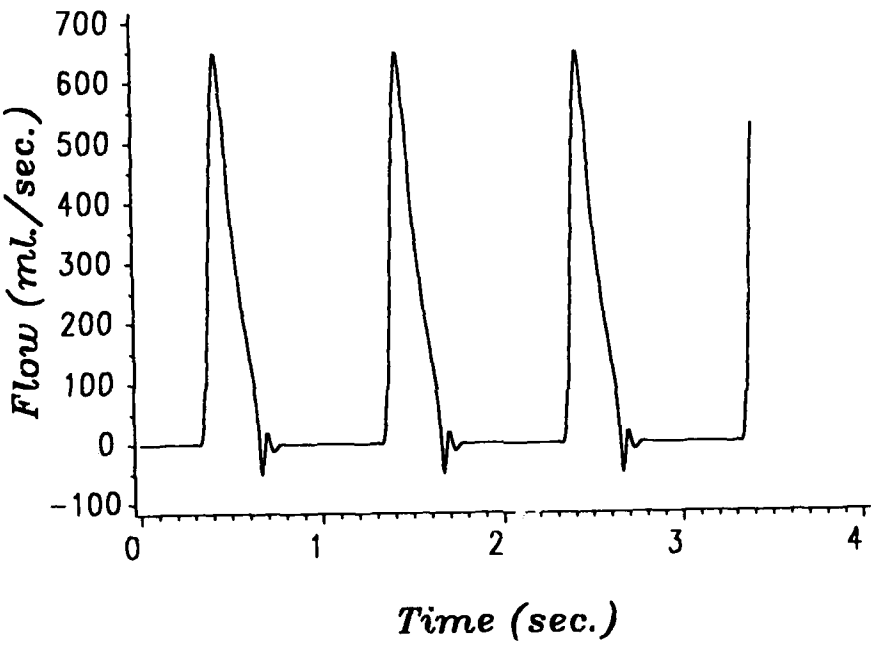

Figure 11: During one cycle of breathing (after Vernon et al.)

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A COMPARTMENTAL BRAIN MODEL FOR CHEMICAL TRANSPORT AND CO_2 CONTROLLED BLOOD FLOW

Shaul Sorek[1], Jacob Bear[2], Moshe Feinsod[3]

ABSTRACT

A compartmental transport model is developed, capable of predicting the evolution of CO_2, HCO_3^- and H^+ in the cerebrovascular system. In the model, the transport of these components is simulated at a subset of three compartments: CSF, Capillary–Choroid Plexus and Brain Tissue, belonging to a seven compartmental assembly representing the entire brain. The remaining ones are: Artery, Vein, Venous Sinous and Jugular Bulb.

The model accounts for advection associated with non steady perfusion fluxes across semi-pervious boundaries. Pressures, associated with perfusion, are solved separately in the seven compartment model. The three compartment transport model also takes into account changes in compartmental volume, due to displacement of its boundaries, diffusion through boundaries and rate of generation of substances by chemical reactions. A first order reaction rate is assumed in the Brain Tissue compartment. A parameter estimation method is then developed to assess boundary diffusivities from time averaged observed values of perfusion pressure, tension of carbon dioxide, pH values and concentration of free hydrogen and bicarbonate ions. An equation of state for the arteries to capillaries influx, as a function of CO_2 tension in the CSF, is then suggested as a blood flow controller for CO_2 excitations. Upon solving all coupled mass balance equations, and for a pre-evaluated perfusion pressures in the artery and capillary compartments, one can estimate the change in arteries to capillaries conductance at every time step.

Keywords: Compartmental system, non steady perfusion fluxes, compliance, conductance, diffusion, advection, chemical reactions, molecular carbon dioxide, bicarbonate ion, hydrogen ion, parameter estimation.

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INTRODUCTION

Experiments (Greenberg et al. 1978) show that the flow of blood from the *arteries* to the *capillaries* within the cerebrovascular system, is controlled by changes in the concentration of carbon dioxide (CO_2) within the brain tissue. In order to investigate changes in this flow, in response to changes in CO_2 concentration, a model that simulates chemical transport and blood flow in the brain system, was constructed. Following earlier works by the authors (Karni et al. 1987, Sorek et al. 1988a-1988c), a multicompartmental model was selected for this purpose. In such a model, each part of the brain, identified by a certain function that it fulfills, is simulated as a compartment characterized by unique values of time dependent variables, such as pressure and concentration of considered chemical components. Adjacent compartments interact with each other, enabling flow of fluids (here blood) and chemicals (e.g. CO_2 dissolved in the blood) to be transported across intercompartmental boundaries. Mechanisms of species transport include perfusion with the blood and molecular diffusion. In addition, various chemical reactions involving CO_2, HCO_3^- and H^+ take place, affecting their concentration. A model of this kind is often referred to as a *fully mixed, lumped parameter model.*

Following Sorek et al. (1988a) a model composed of seven compartments was constructed to simulate the following brain parts: Artery (A), Capillary and Choroid Plexus (C), Venous (V), Venous Sinus (S), Jugular Bulb (J), Cerebrovascular Fluid (F) and Brain Tissue (B).

In the model investigated here, it is assumed that a single (averaged) incompressible fluid flows through the various compartments that simulate the cerebral system. The mathematical model is comprised of mass and momentum balance equations for the fluid and mass balance equations for each of the chemical substances influencing the CO_2-transport.

THE LUMPED PARAMETER FLOW MODEL

Figure 1 shows three adjacent compartments; (i), (j) and (n), separated by common boundaries which permit fluid to leak through them, from (i) into (n) and from (n) into (j). They also allow components dissolved in the fluid to be transported across the boundaries. The solute is transported through any boundary by two mechanisms: advection with the fluid, commonly

referred to as transport by *perfusion*, and molecular diffusion. The boundary itself acts as a semi-pervious membrane which can be displaced in response to pressure changes in the adjacent compartments. This displacement produces changes in the volume of each compartment. We use the term *compliance* to describe the relation between the change in a compartment's volume to the change in the pressure difference across it.

For a fluid of constant density, ρ, the mass balance for the (n)th compartment is expressed by

$$\sum_{i=1}^{I_{(n)}} q_{in} - \sum_{j=1}^{J_{(n)}} q_{nj} + Q_{(n)} = \frac{dV_n}{dt} \tag{1}$$

where $I_{(n)}$ and $J_{(n)}$ denote the number of compartments from which flow enters the (n)th compartment, and leaves it, respectively, q_{in} and q_{nj} denote the fluxes from the (i)th compartment into the (n)th one, and from the (n)th one to the (j)th one, respectively, $Q_{(n)}$ denotes the fluid sources in the (n)th compartment, and V_n denotes the volume of compartment (n). The compartmental volume is affected by the rigidity of the displaced boundary in response to changes in the pressure difference $p_{mn} (= p_m - p_n)$ across the mutual boundary between compartments (m) and (n).

Within the cerebral system, differences in elevation, H, are small. Hence, we may assume that between two compartments, m and n, we have

$$p_{mn} \equiv (p_m - p_n) \gg \rho g (H_m - H_n) \tag{2}$$

where g denotes the gravity acceleration.

The flux through a semi-pervious boundary between two compartments is proportional to the piezometric (≡ hydraulic) head difference between them. However, in view of (2), we assume proportionality to the pressure difference, i.e.

$$q_{in} = Z_{in}\, p_{in} \tag{3}$$

where Z_{in} is called the *conductance* of the boundary between the (i)th and (n)th compartments. The rate of change in V_n appearing in (1) is expressed by

$$\frac{dV_n}{dt} = \sum_{m=1}^{M_{(n)}} \frac{dV_n}{dP_{mn}} \cdot \frac{dP_{mn}}{dt} = \sum_{m=1}^{M_{(n)}} C_{mn} \frac{dP_{mn}}{dt} \tag{4.1}$$

where C_{nm} denotes the value of the compliance of the (n)th compartment due to the displacement of its boundary with the (m)th one, and $M_{(n)}$ is the number of boundaries of compartment (n) that are associated with a compliance.

The compliance, C_{nm}, is defined by

$$C_{nm} = \frac{dV_n}{dp_{nm}} \ . \tag{4.2}$$

In view of (3) and (4), we can now rewrite (1) in the form

$$Q_{(n)} = -\sum_{i=1}^{I_{(n)}} Z_{in}\, p_{in} + \sum_{j=1}^{J_{(n)}} Z_{nj}\, p_{nj} + \sum_{m=1}^{M_{(n)}} C_{nm} \frac{dP_{nm}}{dt} \tag{5}$$

In general, the various Z's and C_{nm}'s are assumed constant. In this paper (as in earlier papers by the authors (Sorek et al. 1988a-1988c), these coefficients are allowed to vary as functions of time e.g., in the form of a step function in time, say, in response to illness. As will be shown in the section below, the conductance between the arteries and the capillaries, depends on the pressure differences, P_{AC}.

Equation (5) constitutes a set of n equations, one for each of the n compartments, in the n unknown pressures, P_n.

TRANSPORT OF CHEMICAL COMPONENTS

Our next objective is to formulate the mass balance equation for the chemical components transported through the compartmental system.

We make the assumption that the concentrations of the various chemical components and the various coefficients that govern transport and chemical reactions are independent of the pressure. This makes the problem of pressure variations in the compartments independent of the problem of concentration distribution. Accordingly, the former problem can be solved first, using the resulting pressures as input to the latter one. In fact, the authors have already addressed the

problem of pressure distribution in earlier papers (Sorek et al. (1988a,b)).

A detailed literature survey on the effect of changes in arterial carbon dioxide tension on cerebral blood flow is documented in Greenberg et al. (1978). In that work, a mathematical model is developed that relates the cerebral blood flow control to changes of CO_2 tension in the arteries ($P_a CO_2$). Greenberg's model of the controlled perfusion in the brain system is composed of three compartments: capillaries (blood), *cerebral extracellular fluid and cerebral intracellular fluid*. His model is based on the assumption of rigid compartmental walls and constant perfusions blood pressure.

In what follows, we present a modification and an extension of Greenberg's model. The extra/intro cellular fluid compartments are lumped into one brain tissue compartment. We relax the assumption of rigid walls by introducing compliances and by solving the perfusion pressure for a *nonsteady system*.

The general layout, composed of a seven-compartment system, is shown in Figure 2. This general system was developed by Sorek et al. (1988a) to evaluate changes in the cerebral perfusion pressure. Figure 3 shows the transport as conceived by Davson (1967) and Greenberg et al. (1978). Our aim is to include in the model the regulation of arterial to capillary conductance as a *function of* CO_2, *pressure* associated with perfusion flux and changes in compartment volume related to boundary compliance.

Following the discussion of Greenberg et al. (1978), we focus our attention on the hydration reaction that takes place in the physiologic fluid circulating through the cerebrovascular system

$$CO_2 + H_2O \underset{\kappa_R}{\overset{\kappa_f}{\rightleftharpoons}} H^+ + HCO_3^- \ . \tag{6}$$

This chemical reaction influences the transport of dissolved CO_2 and will thus be considered in the model. The coefficients κ_f and κ_R are the forward and reverse rate constants, respectively.

In view of (6), the three chemical species that are involved in controlling the blood flow are: molecular carbon dioxide (CO_2), bicarbonate ion (HCO_3^-) and the hydrogen ion (H^+).

In developing the transport equations, we write a mass balance equation for each of these substances, using the notation: $l = 1$ for CO_2, $l = 2$ for HCO_3^- and $l = 3$ for H^+.

For the mixed cell idealization considered here, with no external sources or sinks of the components, the mass balance for the l substance in compartment n, is expressed by

$$\frac{d}{dt}(c_n^l V_n) = \sum_{i=1}^{I_{(n)}} c_{i(n)}^l \, q_{in} - c_n^l \sum_{j=1}^{J_{(n)}} q_{nj} + \sum_{k=j}^{K_{(n)}} D_{kn}^l + R_n^l \tag{7}$$

where c_n^l is the concentration i.e., mass of species l *per unit volume of compartment* n, R_n^l denotes the rate of production of the lth substance by chemical reaction in the n th compartment. $c_{i(n)}^l$ is the concentration of species l in cell i entering cell n, D_{kn}^l is the flux by diffusion of the substance l from compartment k into cell n through their common boundary (a total of $K_{(n)}$ such boundaries). The perfusion fluxes, q_{in} and q_{nj}, are related to the pressure difference by (3). As the pressure fluctuates, these advective fluxes, that carry solutes, also fluctuate in magnitude. In most existing models, these fluxes are assumed constant. For example, the flux from the arteries to the capillaries, which affects the corresponding solute transport, varies in the range ±5% (for an average of 750 ml/min; (Sorek et al. 1988b)). The diffusive flux is expressed by

$$D_{kn}^l = \mathcal{D}_{kn}^l \, (c_{k(n)}^l - c_n^l) \tag{8}$$

where $\mathcal{D}_{kn}^l$ is a coefficient that is related to the diffusivity and "thickness" of the boundary, thus regarded as *boundary diffusivity*. By expanding the first term of (7) and in view of (4), we obtain

$$\frac{d}{dt}(c_n^l V_n) = \left[\sum_{m=1}^{M_{(n)}} C_{nm} \frac{dP_{nm}}{dt}\right] c_n^l + \bar{V}_n \frac{dc_n^l}{dt} \; . \tag{9}$$

By integrating (4.2), we use the symbol $\bar{V}_n$, for

$$\bar{V}_n \equiv \overset{0}{V}_n + \sum_{m=1}^{M_{(n)}} (\hat{V}_{nm} + C_{nm} P_{nm}) \tag{10}$$

where

$$\hat{V}_{nm} \equiv C_{nm} (\overset{0}{P}_n - \overset{0}{P}_m) \tag{11}$$

and $\overset{0}{V}_n$, $\overset{0}{P}_n$, $\overset{0}{P}_m$ are reference values given at the same time (e.g., at t=0).

If we now substitute (3), (8)-(11) into (7) we obtain

$$\bar{V}_n \frac{dc_n^l}{dt} = \sum_{i=1}^{I_{(n)}} Z_{in} P_{in} c_{i(n)}^l + \\ - c_n^l \left[\sum_{j=1}^{J_{(n)}} Z_{nj} p_{nj} + \sum_{m=1}^{M_{(n)}} C_{nm} \frac{dP_{nm}}{dt} \right] + \sum_{k=1}^{K_{(n)}} \mathcal{D}_{kn}^l (c_{k(n)}^l - c_n^l) + R_n^l \,. \tag{12}$$

Then, by multiplying (5) by c_n^l, and subtracting from (12), we obtain

$$\bar{V}_n \frac{dc_n^l}{dt} = \sum_{i=1}^{I_{(n)}} Z_{in} (c_{i(n)}^l - c_n^l) P_{in} + \sum_{k=1}^{K_{(n)}} \mathcal{D}_{kn}^l (c_{k(n)}^l - c_n^l) - c_n^l Q_{(n)} + R_n^l \,. \tag{13}$$

Henry's law states that the concentration of a dissolved gas (e.g. CO_2) in a fluid is related to its solubility, α^l, by

$$c_n^l = \alpha^l \pi_n^l \tag{14}$$

where α^l (constant for all cells) is in moles/liter/mmHg and π_n^l is partial pressure of the gas in cell n. In writing (14), we have overlooked the difference between the volume of a cell and the volume of fluid in it, assuming that the volume of (solid) tissue in the cell is negligible.

Thus, in view of (14), the mass balance equation (13) for the dissolved gas, becomes

$$\bar{V}_n \frac{d\pi_n^l}{dt} = \sum_{i=1}^{I_{(n)}} Z_{in} \pi_{in}^l P_{in} + \sum_{k=1}^{K_{(n)}} \mathcal{D}_{kn}^l \pi_{kn}^l - \pi_n^l Q_{(n)} + R_n^l / \alpha^l \tag{15}$$

where $\pi_{in}^l \equiv \pi_i^l - \pi_n^l$. Note that (15) does not include any efflux terms.

In view of the transport processes depicted in Figure 2 and (15), we write the explicit forms of the mass balance equations for dissolved CO_2 in the C, F and B compartments

Capillary and Choroid Plexus

$$C: \quad \bar{V}_C \frac{d\pi_C^1}{dt} = Z_{AC} \pi_{AC}^1 P_{AC} + \mathcal{D}_{BC}^1 \pi_{BC}^1 + \mathcal{D}_{FC}^1 \pi_{FC}^1 + R_C^1 / \alpha^1 \tag{16.1}$$

$$\bar{V}_C = \mathring{V}_C + \hat{V}_{CF} + C_{CF} P_{CF} \tag{16.2}$$

where $(\hat{V}_{CF} + C_{CF} P_{CF}) / \mathring{V}_C \cong 5\%$ (Sorek et al. 1988a).

CSF

$$F: \quad \bar{V}_F \frac{d\pi_F^1}{dt} = (Z_{CF} P_{CF} + \mathcal{D}_{FC}^1)\pi_{CF}^1 + \mathcal{D}_{BF}^1 \pi_{BF}^1 + R_F^1/\alpha^1 \tag{17.1}$$

$$\bar{V}_F = \overset{o}{V}_F + \hat{V}_{FC} + \hat{V}_{FB} + \hat{V}_{FS} + C_{CF}P_{FC} + C_{FB}P_{FB} + C_{FS}P_{FS} \tag{17.2}$$

where $(\hat{V}_{FC} + \hat{V}_{FB} + \hat{V}_{FS} + C_{CF}P_{FC} + C_{FB}P_{FB} + C_{FS}P_{FS})/\overset{o}{V}_F \cong 1.5\%$

Brain Tissue

$$B: \quad \bar{V}_B \frac{d\pi_B^1}{dt} = (Z_{CB} P_{CB} + \mathcal{D}_{BC}^1)\pi_{CB}^1 + (Z_{FB} P_{FB} + \mathcal{D}_{BF}^1)\pi_{RB}^1 + R_B^1/\alpha \tag{18.1}$$

$$\bar{V}_B = \overset{o}{V}_B + \hat{V}_{BV} + \hat{V}_{BF} + C_{BV}P_{BV} + C_{FB}P_{BF} \tag{18 2}$$

where $(\hat{V}_{BV} + \hat{V}_{BF} + C_{BV}P_{BV} + C_{FB}P_{BF})/\overset{o}{V}_B \cong 0.1\%$. We note the trend in the effect of the compliances on the CO_2 concentration changes.

With (15) as a typical balance equation for gas such as CO_2 in a compartment, expressed in terms of the partial gas pressure π, we write seven balance equations for the seven compartments. Compartment A serves as a compartment with known fluid pressure and partial gas pressure that represent boundary conditions. This leaves only six compartments and six CO_2 balance equations. By examining Figure 2, we note that the three compartments, C, F and B, contain no influx, excluding the flux from A into C. Hence, in view of (15), we may write a subsystem of three balance equations for the C, F and B cells in terms of the variables π_C^1, π_F^1 and π_B^1. This subset of equations is independent of what happens in the remaining three compartments V, S and J. Actually, in order to decouple this subset of equations from the remaining equations, we had to introduce one more simplifying assumption. This assumption states that the advective CO_2 fluxes between the adjacent compartments from A to C, from C to V, and from B to V, are much larger than the diffusion fluxes between the same compartments. In each case, we may express this assumption by a Peclet number, $P_e = \vartheta L/D$, that expresses the ratio between the advective and diffusive fluxes, where ϑ is the mean fluid velocity crossing

the appropriate boundary, D is the coefficient of diffusion and L is a characteristic distance between the projection of compartment centers on the line perpendicular to the common boundary.

In the compartmental balance equations, the Peclet number is expressed in the form

$$P_{e_c} = \frac{Z_{in}\, P_{in}}{\mathcal{D}_{in}} \tag{19}$$

Hence, when $P_{e_c} \to \infty$, the advective flux is dominant, while $P_{e_c} \to 0$ means the domination of the diffusive flux. When $0 < P_{e_c} < \infty$, we have to include both the advective and diffusive fluxes.

Our next objective is to write the balance equation for HCO_3^- for the C, F and B compartments. Here we have to take into account the ionic nature of this component. In addition to diffusion across the boundary between adjacent cells, as driven by a concentration difference, another diffusive flux is produced by the difference in electric potential across the boundary. These differences in electrical potential result from the behavior of boundaries as semi-pervious membranes which prevent certain ions from passing through them (Greenberg et al. 1978). Because of the electrical charges, and because we deal with the diffusive flux of charged particles (viz, the HCO_3^- ion) the membrane itself becomes charged and affects the diffusive flux through it.

Nernst's equation describes the *equilibrium* potential created by the ion distributions across the membrane.

The diffusion of an ion through a charged membrane as governed by the electrochemical potential was formulated by Harris (Harris, 1960).

Typical measured values of the electrical potential across membranes for bicarbonate and hydrogen ions (Messeter and Siesjo, 1971; Sorensen, 1971) do not agree with values as calculated by the Nernst equation. This leads to the conclusion that the Nernst equation does not describe the equilibrium in electro-chemical potentials across a membrane boundary in the cerebral fluids, as produced by the concentrations of HCO_3^- and H^+ ions on both sides of such boundary. Greenberg (1978) addresses this issue and suggests an additional diffusive term, controlled by a coefficient of diffusion $\mathcal{D}''$.

In what follows, we follow Greenberg's (1978) development, when applying the component balance equation (13) to HCO_3^- in the C, F and B compartments.

Capillary and Choroid Plexus

$$C: \quad \bar{V}_C \frac{dc_C^2}{dt} = Z_{AC}(c_A^2 - c_C^2)P_{AC} + \mathcal{D}_{BC}^2(c_B^2 - \gamma_{BC}^2 c_C^2) + \mathcal{D}_{FC}^2(c_F^2 - \gamma_{FC}^2 c_C^2) + R_C^2 \tag{20.1}$$

where

$$\left.\begin{aligned} \mathcal{D}_{BC}^2 &= \mathcal{D}_{BC}^{'2} + \mathcal{D}_{BC}^{''2} \\ \gamma_{BC}^2 &= \frac{\mathcal{D}_{BC}^{'2}}{\mathcal{D}_{BC}^2} \cdot \exp(-\frac{fZ}{RT} E_m) \end{aligned}\right\} \tag{20.2}$$

$$\left.\begin{aligned} \mathcal{D}_{FC}^2 &= \mathcal{D}_{FC}^{'2} + \mathcal{D}_{FC}^{''2} \\ \gamma_{FC}^2 &= \frac{\mathcal{D}_{FC}^{'2}}{\mathcal{D}_{FC}^2} \cdot \exp(-\frac{fZ}{RT} E_m) \end{aligned}\right\} \tag{20.3}$$

In these equations f is Faraday constant, Z is the valence of ion, R is gas constant, T is absolute temperature and E_m is the maximum equilibrium potential according to the Nernst equation

$$E_m = 61.5 \log \frac{c'}{c''} \tag{21}$$

where c' and c'' are concentrations on both sides of the membrane.

CSF

$$F: \quad \bar{V}_F \frac{dc_F^2}{dt} = Z_{CF}(c_C^2 - c_F^2)P_{CF} + \mathcal{D}_{FC}^2(\gamma_{FC}^2 c_C^2 - c_F^2) + \mathcal{D}_{BF}^2(c_B^2 - \gamma_{BF}^2 c_F^2) + R_F^2 \tag{22}$$

Here $\mathcal{D}_{FC}^2$, γ_{FC}^2, $\mathcal{D}_{BF}^2$ and γ_{BF}^2 are similar in their expression in (20.2), (20.3).

Brain Tissue

$$B: \quad \bar{V}_B \frac{dc_B^2}{dt} = Z_{CB}(c_C^2 - c_B^2)P_{CB} + Z_{FB}(c_F^2 - c_B^2)P_{FB} + \\ + \mathcal{D}_{BC}^2(\gamma_{BC}^2 c_C^2 - c_B^2) + \mathcal{D}_{BF}^2(\gamma_{BF}^2 c_F^2 - c_B^2) + R_B^2 \tag{23}$$

Note that from (6), it follows that

$$R_n^1 = -R_n^2 = -R_n^3 \qquad n = B, C, F \tag{24}$$

provided that the R's are expressed in moles. Otherwise, an appropriate conversion must be introduced (say, from moles to grams). Note that (24) constitutes two equations for each compartment. The concentration of water is assumed constant so that it has no rate of production.

In the case of the Hydrogen ion, we realize that a considerable quantity of the formed H^+ becomes bound to various buffers (to hemoglobin in the blood). The bound portion of the total amount does not contribute changes in pH which is a measure of the (non-bound) concentration of H^+ in the fluid. We define a *buffer capacity*, β, of a homogeneous medium by the rise in total hydrogen ion concentration, c^{3t}, per unit rise in pH, i.e.

$$\beta = \frac{dc^{3t}}{dpH} \tag{25}$$

The definition of pH ($= -\log c^3$), together with (25) yields

$$\frac{dc^{3t}}{dt} = \frac{-\beta}{(\ln 10)c^3} \frac{dc^3}{dt} \tag{26}$$

The integration of (25) for compartments n and i (assuming β to be constant within the range encountered in the compartments) yields

$$c_i^{3t} - c_n^{3t} = \beta(pH_i - pH_n) - (B_n - B_i) \tag{27}$$

where B_n and B_i are integration constants associated with compartments n and i, respectively.

The discussion presented above on the diffusion of the bicarbonate ion across boundaries between adjacent compartments is also applicable to the hydrogen ions.

In view of (12), (26) and (27), we write the balance equations for the H^+ ion in compartments C, F and B.

Capillary and Choroid Plexus

$$C: \quad \bar{V}_C \frac{dc_C^3}{dt} = -\frac{ln\ 10}{\beta} c_C^3 \{ Z_{AC}(\beta pH_{AC} - B_{CA})P_{AC} + \\ + \mathcal{D}_{BC}^3(c_B^3 - \delta_{BC}^3 c_C^3) + \mathcal{D}_{FC}^3(c_F^3 - \delta_{FC}^3 c_C^3) - R_C^3 \} \tag{28.1}$$

where

$$\left.\begin{aligned} \mathcal{D}_{BC}^3 &\equiv \mathcal{D}_{BC}^{'3} \\ \delta_{BC}^3 &= \frac{\mathcal{D}_{BC}^{'3} \exp(E_m \frac{fZ}{RT}) + \mathcal{D}_{BC}^{''3}}{\mathcal{D}_{BC}^3} \end{aligned}\right\} \tag{28.2}$$

$$\left.\begin{aligned} \mathcal{D}_{FC}^3 &\equiv \mathcal{D}_{FC}^{'3} \\ \delta_{FC}^3 &= \frac{\mathcal{D}_{FC}^{'3} \exp(E_m \frac{fZ}{RT}) + \mathcal{D}_{FC}^{''3}}{\mathcal{D}_{FC}^3} \end{aligned}\right\} \tag{28.3}$$

Here $pH_{ij} \equiv pH_i - pH_j$ and $B_{ij} \equiv B_i - B_j$.

CSF

$$F: \quad \bar{V}_F \frac{dc_F^3}{dt} = -\frac{\ln 10}{\beta} c_F^3 \{ Z_{CF}(\beta pH_{CF} - B_{FC})P_{CF} + \\ + \mathcal{D}_{FC}^3(\delta_{FC}^3 c_C^3 - c_F^3) + \mathcal{D}_{BF}^3(c_B^3 - \delta_{BF}^3 c_F^3) - R_F^3 \} \tag{29}$$

Here $\mathcal{D}_{FG}^3$, δ_{FC}^3, $\mathcal{D}_{BF}^3$, and δ_{BF}^3 have expressions similar to those given in (28.2) and (28.3).

Brain Tissue

$$B: \quad \bar{V}_B \frac{dc_B^3}{dt} = -\frac{\ln 10}{\beta} c_B^3 \{ Z_{CB}(\beta p H_{CB} - B_{BC}) P_{CB} + Z_{FB}(\beta p H_{FB} - B_{BF}) P_{FB} + \\ + \mathcal{D}_{BG}^3(\delta_{BC}^3 c_C^3 - c_B^3) + \mathcal{D}_{BF}^3(\delta_{BF}^3 c_F^3 - c_B^3 - R_B^3) \} \tag{30}$$

The presence of the enzyme carbonic anhydrase in the red blood cells makes the hydration/dehydration practically instantaneous. Consequently reaction (6) is always one of equilibrium, described by the reaction constant κ.

On the other hand, in compartment B, the absence of carbonic anhydrase in the cerebral extracellular fluid means that reaction is not one of equilibrium. Instead, it has a finite constant rate. We assume a first order reaction in which the rate is proportional to the concentration. Under conditions of non-equilibrium, the rate of production of CO_2 equals the difference between the reverse and forward reaction rates. Therefore, in view of (6) and (14), we write for the B compartment

$$R_B^1 = \bar{V}_B(\kappa_R c_B^3 c_B^2 - \kappa_f \alpha^1 \pi_B^1) \tag{31}$$

In compartments C and F, where the reaction is in equilibrium, we write

$$\kappa = \frac{c^3 c^2}{c^1} \tag{32}$$

Concentration of water (H_2O) is assumed constant, hence it is incorporated in the reaction constant κ. By virtue of (14) and (32) we conclude that $c^3 = c^3(\alpha^1\pi^1, c^2)$. Therefore, we can replace (32) for compartments C and F, by the relation

$$\frac{dc^3}{dt} = -\frac{\alpha^1 \kappa \pi^1}{(c^2)^2} \frac{dc^2}{dt} + \frac{\alpha^1 \kappa}{c^2} \frac{d\pi^1}{dt} \tag{33}$$

At this stage we have a model consisting of 18 unknown variables:

$$c_n^l \text{ and } R_n^l \; ; \; n = B, C, F; \; l = 1, 2, 3$$

for which we have 18 coupled equations:

nine component balance equations, one for each component in each compartment.

two equations (33) for compartments C and F and equation (31) for compartment B, and

three times equations (24), one for each compartment.

In principle, a solution can be obtained.

We note that this set of coupled equations is non-linear. The coupling is through the rate of production terms (R_n^l).

In the above set of equations we encounter various coefficients, or parameters. One group consists of coefficients such as κ_f , κ_R , f $\cdots$ that are universal and assumed known. They are independent of the particular model employed here. The second group consists of the conductances Z_{ni}, compliances C_{ni} and boundary diffusivities $\mathcal{D}_{ni}^l$. The determination of the coefficients Z_{ni} and C_{ni} was described in an earlier paper (Sorek et al. 1988a,c) and will be considered here as already known.

In the following section, we shall consider the determination of the various boundary diffusivities of the model.

ESTIMATING DIFFUSION COEFFICIENTS

In view of (16) to (18), we may write the CO_2 balance equations, in a matrix form

$$\underline{\underline{\bar{V}}} \frac{d\underline{\pi}^1}{dt} + \underline{\underline{\mathcal{D}}}^1 \underline{\pi}^1 = \underline{B}^1 + \underline{R}^1/\alpha^1 \tag{34}$$

where

$$\underline{\pi}^1 = [\pi_C^1, \pi_F^1, \pi_B^1]^T \tag{35.1}$$

$$\underline{\underline{\bar{V}}} = \begin{bmatrix} \bar{V}_C & & \\ & \bar{V}_F & \\ & & \bar{V}_B \end{bmatrix} \tag{35.2}$$

$$\underline{\underline{\mathcal{D}}}^1 = \begin{bmatrix} (Z_{AC}P_{AC} + \mathcal{D}^1_{BC} + \mathcal{D}^1_{FC}) & -\mathcal{D}^1_{FC} & -\mathcal{D}^1_{BC} \\ -(Z_{CF}P_{CF} + \mathcal{D}^1_{FC}) & (Z_{CF}P_{CF}+\mathcal{D}^1_{FC}+\mathcal{D}^1_{BF}) & -\mathcal{D}^1_{BF} \\ -(Z_{CB}P_{CB} + \mathcal{D}^1_{BC}) & -(Z_{FB}P_{FB}+\mathcal{D}^1_{BF}) & (Z_{CB}P_{CB}+Z_{FB}P_{FB}+\mathcal{D}^1_{BC}+\mathcal{D}^1_{BF}) \end{bmatrix}$$

(35.3)

$$\underline{B}^1 = [Z_{AC}P_{AC}\pi^1_A,\ 0,\ 0]^T \tag{35.4}$$

$$\underline{R}^1 = [R^1_C, R^1_F, R^1_B]^T \tag{35.5}$$

Similarly, in view of (20) to (23) we write the balance equations for the HCO_3^- element

$$\underline{\underline{V}}\ \frac{d\underline{c}^2}{dt} + \underline{\underline{\mathcal{D}}}^2\underline{c}^2 = \underline{B}^2 + \underline{R}^2 \tag{36}$$

where,

$$\underline{c}^2 = [c^2_C,\ c^2_F,\ c^2_B\ ]^T \tag{37.1}$$

$$\underline{\underline{\mathcal{D}}}^2 = \begin{bmatrix} (Z_{AC}P_{AC}+\mathcal{D}^2_{BC}\gamma^2_{BC}+\mathcal{D}^2_{FC}\gamma^2_{FC}) & -\mathcal{D}^2_{FC} & -\mathcal{D}^2_{BC} \\ -(Z_{CF}P_{CF}+\mathcal{D}^2_{FC}\gamma^2_{FC}) & (Z_{CF}P_{CF}+\mathcal{D}^2_{FC}+\mathcal{D}^2_{BF}\gamma^2_{BF}) & -\mathcal{D}^2_{BF} \\ -(Z_{CB}P_{CB}+\mathcal{D}^2_{BC}\gamma^2_{BC}) & -(Z_{FB}P_{FB}+\mathcal{D}^2_{BF}\gamma^2_{BF}) & (Z_{CB}P_{CB}+Z_{FB}P_{FB}+\mathcal{D}^2_{BC}+\mathcal{D}^2_{BF}) \end{bmatrix}$$

(37.2)

$$\underline{B}^2 = [Z_{AC}P_{AC}c^2_A,\ 0,\ 0]^T \tag{37.3}$$

$$\underline{R}^2 = [R^2_C, R^2_F, R^2_B]^T \tag{37.4}$$

Obviously the solution of the model requires appropriate initial condition. Examination of the matrix forms (35.3) and (37.2) indicates that they are non-singular, which means that a solution is possible. This is due to the fact that the model involves both diffusion and perfusion.

The CO_2 concentration (like those of HCO_3^- and H^+) continuously undergoes changes. These changes are introduced both by the person's behavior and by various environmental

factors, e.g., temperature. On the other hand, various control mechanisms exist in the brain that continuously act to restore some average or normal concentration.

As the CO_2 mass (as well as that of HCO_3^- and H^+) within each compartment varies, we may identify points in time, say, t_1 and t_2 ($>t_1$), at which this mass is the same. This means that over that time interval (regardless of the sequence of changes inbetween those points), $t_2 - t_1$, the total mass of CO_2 in the compartment has not changed. Hence

$$\int_{t_1}^{t_2} \bar{V} \frac{\partial c}{\partial t} dt = 0 \; ; \; \bar{V}c|_{t_1} = \bar{V}c|_{t_2}$$

Thus by integrating (34) and (36) over a period of time beginning and ending with the same component mass, we obtain accordingly

$$\underline{\underline{\mathcal{D}}}^1 \underline{\bar{\pi}}^1 = \underline{\bar{B}}^1 + \underline{\bar{R}}^1/\alpha^1 \tag{38}$$

$$\underline{\underline{\mathcal{D}}}^2 \underline{\bar{c}}^2 = \underline{\bar{B}}^2 + \underline{\bar{R}}^2 \tag{39}$$

where ($\bar{}$) denotes a value averaged over the considered time period. Eq. (39) reformulated to solve the inverse problem for the diffusion parameters $\underline{\underline{\mathcal{D}}}^1$, take the form

$$\underline{\underline{\bar{\pi}}}^1 \underline{\mathcal{D}}^1 = \underline{L}^1 \tag{40}$$

where

$$\underline{\mathcal{D}}^1 = [\mathcal{D}^1_{BC}, \mathcal{D}^1_{FC}, \mathcal{D}^1_{BF}]^T \tag{41.1}$$

$$\pi^1 = \begin{bmatrix} \bar{\pi}^1_{CB} & \bar{\pi}^1_{CF} & 0 \\ 0 & \bar{\pi}^1_{FC} & \bar{\pi}^1_{FB} \\ \bar{\pi}^1_{BC} & 0 & \bar{\pi}^1_{BF} \end{bmatrix} \tag{41.2}$$

$$\underline{L}^1 = [(Z_{AC}\bar{\pi}^1_{AC}\bar{P}_{AC} + \frac{\bar{R}^1_C}{\alpha^1}), (Z_{CF}\bar{\pi}^1_{CF}\bar{P}_{CF} + \frac{\bar{R}^1_F}{\alpha^1}), (Z_{CB}\bar{\pi}^1_{CB}\bar{P}_{CB} + Z_{FB}\bar{\pi}^1_{FB}\bar{P}_{FB} + \frac{\bar{R}^1_B}{\alpha^1})]^T \tag{41.3}$$

where $\tilde{\pi}_{ij} (\equiv \tilde{\pi}_i - \tilde{\pi}_j)$ and $\tilde{P}_{ij} (\equiv \tilde{P}_i - \tilde{P}_j)$ are differences between time averaged values of

CO_2 tension and pressures associated with perfusion fluxes, respectively.

We note that in (40), the terms expressing the perfusion fluxes have been incorporated in the $\underline{L}$ matrix, as they are assumed known (from the solution of the flow problem in which all flow parameters are known, Sorek et al. 1988a). However, from the point of view of diffusion, the three compartments act as a closed system, the equations describing diffusion alone cannot be solved unless we bring in additional information , e.g. initial conditions. Mathematically these considerations manifest themselves by the fact that the matrix in (41.2) is singular. As additional information let us assume that

$$\mathcal{D}^1_{BC} = K^1 \tag{42}$$

where K^1 is a known value.

By virtue of (40) to (42) we obtain

$$\mathcal{D}^1_{FC} = -\frac{1}{\tilde{\pi}^1_{CF}} \cdot [Z_{CF}\tilde{P}_{CF}\tilde{\pi}^1_{CF} + (Z_{CB}\tilde{P}_{CB}+K^1)\tilde{\pi}^1_{CB} + Z_{FB}\tilde{P}_{FB}\tilde{\pi}^1_{FB} + \frac{1}{\alpha^1}(\tilde{R}^1_F+\tilde{R}^1_B)] \tag{43}$$

$$\mathcal{D}^1_{BF} = -\frac{1}{\tilde{\pi}^1_{FB}} [(Z_{CB}\tilde{P}_{CB}+K^1)\tilde{\pi}^1_{CB} + Z_{FB}\tilde{P}_{FB}\tilde{\pi}^1_{FB} + \frac{\tilde{R}^1_B}{\alpha^1}] \tag{44}$$

Similarly the inverse problem for HCO_3^- is solved by

$$\underline{\underline{C}}^2\,\underline{\mathcal{D}}^2 = \underline{L}^2 \tag{45}$$

where

$$\underline{\mathcal{D}}^2 = [\mathcal{D}^2_{BC}, \mathcal{D}^2_{FC}, \mathcal{D}^2_{BF}]^T \tag{46.1}$$

$$\underline{\underline{C}}^2 = \begin{bmatrix} -(c_B^2-\gamma^2_{BC}c_C^2) & -(c_F^2-\gamma^2_{FC}c_C^2) & 0 \\ 0 & -(\gamma^2_{FC}c_C^2-c_F^2) & -(c_B^2-\gamma^2_{BF}c_F^2) \\ -(\gamma^2_{BC}c_C^2-c_B^2) & 0 & -(\gamma^2_{BF}c_F^2-c_B^2) \end{bmatrix} \tag{46.2}$$

$$\underline{L}^2 = [(Z_{AC}\bar{c}_{AC}^2\bar{P}_{AC} + \bar{R}_C^2), (Z_{CF}\bar{c}_{CF}^2\bar{P}_{CF}+\bar{R}_F^2), \\ (Z_{CB}\bar{c}_{CB}^2\bar{P}_{CB} + Z_{FB}\bar{c}_{FB}^2\bar{P}_{FB} + \bar{R}_B^2)] \tag{46.3}$$

where

$$\bar{c}_{ij}^2 \equiv \bar{c}_i^2 - \bar{c}_j^2$$

To allow the solution of (45), we assume, as above, that the value for $\mathcal{D}_{BC}^2$ is known.

$$\mathcal{D}_{BC}^2 = K^2 \tag{47}$$

Hence in view of (45) to (47), we obtain

$$\mathcal{D}_{FC}^2 = \frac{1}{\bar{c}_F^2 - \gamma_{FC}^2\bar{c}_C^2}[Z_{CF}\bar{P}_{CF}\bar{c}_{CF}^2 + Z_{CB}\bar{P}_{CB}\bar{c}_{CB}^2 + Z_{FB}\bar{P}_{FB}\bar{c}_{FB}^2 + \\ + K^2(\gamma_{BC}^2\bar{c}_C^2 - \bar{c}_B^2) - (\bar{R}_F^2 + \bar{R}_B^2)] \tag{48}$$

$$\mathcal{D}_{BF}^2 = \frac{1}{\bar{c}_B^2 - \gamma_{BF}^2\bar{c}_F^2}[Z_{CB}\bar{P}_{CB}\bar{c}_{CB}^2 + Z_{FB}\bar{P}_{FB}\bar{c}_{FB}^2 + K^2(\gamma_{BC}^2\bar{c}_C^2 - \bar{c}_B^2) + \bar{R}_B^2] \tag{49}$$

The non-linear equations (28) to (30) describe the mass balance of H^+($l \equiv 3$) in the C, F and B compartments.

Again, we assume that the mass of the hydrogen ion undergoes continuous changes. The integration of (28) to (30) over a period at the end of which the mass returns to its initial value, will eliminate the time derivative and yield a linear set of equations that take the form

$$\underline{\underline{C}}^3\,\underline{\mathcal{D}}^3 = \underline{L}^3 \tag{50}$$

where

$$\underline{\mathcal{D}}^3 = [\mathcal{D}_{BC}^3, \mathcal{D}_{FC}^3, \mathcal{D}_{BF}^3]^T \tag{51.1}$$

$$\underline{\underline{C}}^3 = \begin{bmatrix} -[c_C^3 c_B^3 - \delta_{BC}^3 (c_C^3)^2] & -[c_C^3 c_F^3 - \delta_{FC}^3 (c_C^3)^2] & 0 \\ 0 & -[\delta_{FC}(c_C^3)^2 - c_C^3 c_F^3] & -[c_C^3 c_B^3 - \delta_{BF}^3 c_C^3 c_F^3] \\ -[\delta_{BC}^3 (c_C^3)^2 - c_C^3 c_B^3] & 0 & -[\delta_{BF}^3 c_C^3 c_F^3 - c_C^3 c_B^3] \end{bmatrix} \tag{51.2}$$

$$\underline{L}^3 = [Z_{AC}(\beta p H_{AC} + B_{AC})\, P_{AC} c_C^3 + R_C c_C^3] \,,$$

$$, [Z_{CF}(\beta p H_{CF} + B_{CF}) P_{CF} c_F^3 + R_F c_F^3] \,, \tag{51.3}$$

$$, [Z_{CB}(\beta p H_{CB} + B_{CB}) P_{CB} c_B^3 + Z_{FB}(\beta p H_{FB} + B_{FB}) P_{FB} c_B^3 + R_B c_B^3]\,]^T$$

To solve for $\underline{\mathcal{D}}^3$ in (50), we assume, as above, that

$$\mathcal{D}_{BG}^3 = K^3 \tag{52}$$

where K^3 is a known value.

By virtue of (50) to (52) we obtain

$$\mathcal{D}_{FC}^3 = \frac{1}{c_C^3 c_F^3 - \delta_{FC}^3 (c_C^3)^2} [Z_{CF}(\beta p H_{CF} + B_{CF}) P_{CF} c_F^3 + Z_{CB}(\beta p H_{CB} + B_{CB}) P_{CB} c_B^2 + \\ + Z_{FB}(\beta p H_{FB} + B_{FB}) P_{FB} c_B^3 - K^3 (c_C^3 c_B^3 - \delta_{BC}^3 (c_C^2)^2) - (R_F^3 c_F^3 + R_B c_B^3)] \tag{53}$$

$$\mathcal{D}_{BF}^3 = \frac{1}{c_C^3 c_B^3 - \delta_{BF}^3 c_C^3 c_F^3} [Z_{CB}(\beta p H_{CB} + B_{CB}) P_{CB} c_B^3 + \\ + Z_{FB}(\beta p H_{FB} + B_{FB}) P_{FB} c_B^3 + K^3 (\delta_{BC}^3 (c_C^3)^2 - c_C^3 c_B^3) + R_B c_B^3] \tag{54}$$

After estimating the diffusion parameters, one still has to consider additional parameters. These are shown in Table 1.

With the known parameters we solve for the transport of CO_2 , HCO_3^- and H^+ in the Capillaries, CSF and Brain Tissue compartments. The transport and flow problems are solved simultaneously.

BLOOD FLOW CONTROL

In writing the balance equation (5), it is usually assumed that the conductances, Z, are independent of time. However, in reality, the values of Z vary continuously in response to certain changes that occur in the cerebrovascular system. In what follows the brain cells are continuously metabolizing, consuming oxygen and producing carbon dioxide. The changes in the CO_2 production are probably the dominant factor in cerebral blood flow control.

We use a relation (Ponten and Siergo, 1966) between CO_2 tension in the CSF (π_F^1), and in the arteries (π_A^1).

$$\pi_F^1 = 8.6 + 0.942\ \pi_A^1 \tag{55}$$

Following Greenberg et al. (1978), we also use the relation between arterial to capillary blood flow, and π_A^1 (Reivich, 1964).

$$q_{AC} \equiv Z_{AC} P_{AC} = 20.9 + \frac{92.8}{1+10570\ (\pi_A^1)^{2.281}} \tag{56}$$

An increase in the amount of CO_2 in the arterial blood bathing the brain causes a dilation of blood vessels and an increase in the blood flow which carries away CO_2 and reestablishes normal conditions.

By combining (55) and (56) we find the relation between π_F^1 and $Z_{AC} P_{AC}$. Thus for any time instance, knowing the solution for the perfusion pressure fall, P_{AC} (i.e., by solving the fluid's flow equations) and CO_2 tension in the CSF, π_F^1, (i.e., by solving the solute transport problem), we find the appropriate arterial-capillary conductance

$$Z_{AC} = \frac{1}{P_{AC}} \left[20.9 + \frac{92.8}{1 + 10570\ (\frac{\pi_F^1 - 8.6}{0.942})^{-2.281}} \right] \tag{57}$$

Hence we find the change of arterial-capillary conductance due to changes in perfusion pressure and CO_2 tension.

SUMMARY AND CONCLUSIONS

A compartmental brain model was developed to describe transport processes of molecular carbon dioxide (CO_2), bicarbonate ion (HCO_3^-) and hydrogen ion (H^+) between Brain Tissue (B), Capillaries – Choroid Plexus (C) and the CSF (F) compartments. The model consists of mass balance equations (i.e. transport equations) accounting for non-steady advection, diffusion and generation of constituents due to chemical reactions.

Balance equations are expressed in tension values, of CO_2, concentration for HCO_3^-, and pH values and free concentration for H^+.

The fluid is assumed to be of a constant density, hence allowing decoupling between the solutions of fluid and of component balance equations. A separate solution is thus obtained for non steady flow through the cerebrovascular system model by seven compartments: Artery, Capillary plus Choroid Plexus, Brain Tissue, CSF, Vein, Venous Sinous and Jugular Bulb. This solution describes the evolution of compartmental perfusion pressure subject to conductances expressing the case of leakage through semi-pervious boundaries and compliances expressing compartmental volume rate of change due to boundary displacements (Sorek et al. 1988a–1988c). The non steady flow governs the advection term in the model describing the transport of chemical components. This enables the study of pathological situations such as different patterns of initial fluxes that give rise to transient periods of transport; and/or changes in conductances and compliances because of occlusions.

Generation of components in the physiological fluid within a compartment, is governed by the stochiometric relation expressing the hydration reaction. Within the capillaries – choroid plexus and the CSF compartments, the reaction is considered to be instantaneous, hence in equilibrium. Within the brain tissue compartment, the production of CO_2 is assumed to equal the difference between the reverse and forward reaction rates.

In order to solve for the different components, we need to know various coefficients. Some of them may be found in different citations. However, most of the boundary diffusivities need still to be estimated. Therefore, we present a parameter estimation method to assess time averaged boundary diffusivities based on time observations of perfusion pressures, CO_2 tension, HCO_3^-

concentration and pH and free H^+ concentration. For future applications, an assessment is still needed of the sensitivity of the transport solution to parameters such as diffusivities, conductances and compliances defined at the compartmental boundaries. For example, based on previous work of the authors (Sorek et al. 1988a–1988c), we note that the relation between temporal volume change (expressed by the product of boundary compliance and perfusion pressure drop – $C_{ij}\,P_{ij}$) and average boundary volume, is much more significant in the capillaries than in the brain tissue.

Diffusivities, compliances and conductances are assumed as step functions in time i.e. they may change from one constant value to another because of reasons such as illness, aging, etc. We relax this assumption for the conductance, Z_{AC}, controlling flow from the arteries to the capillaries. We introduce an equation of state that relates this conductance to perfusion pressure drop between arteries and capillaries and CO_2 tension in the CSF. Hence, Z_{AC} is changing continuously in response to excitations from the perfusion pressure and CO_2 tension. This short time of response of Z_{AC} describes flow control from arteries to capillaries.

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Table 1: Parameters used in the model simulation.
Some values are after Greenberg et al. (1978), others are after Sorek et al. (1988a-1988c) and Karni et al (1987).

Initial Values

$\overset{o}{P}_C$ = 30 mmHg.	$\overset{o}{\pi}_C^1$=47 mmHg.	$\overset{o}{V}_C$ = 2.5% V_T
$\overset{o}{P}_F$ = 10 mmHg.	$\overset{o}{\pi}_F^1$ = 48 mmHg.	$\overset{o}{V}_F$ = 12.5% V_T
$\overset{o}{P}_S$ = 8 mmHg.	$\overset{o}{\pi}_B^1$ = 46 mmHg.	$\overset{o}{V}_B$ = 83% V_T
$\overset{o}{P}_B$ = 9.5 mmHg.		
c_C^2 =	$c_C^3 = 4.4 * 10^{-5} \frac{\text{mEq.}}{\text{liter}}$	V_T = 1200 ml.
$c_F^2 = 24.74 \frac{\text{mEq.}}{\text{liter}}$	$c_F^3 = 4.8 * 10^{-5} \frac{\text{mEq.}}{\text{liter}}$	
c_B^2 =	$c_B^3 = 9.01 * 10^{-5} \frac{\text{mEq.}}{\text{liter}}$	

Averaged Input parameters

π_A^1 = 40 mmHg	$Z_{AC} = 10.7 \frac{\text{ml/min}}{\text{mmHg}}$	$C_{CF} = 0.036 \frac{\text{ml.}}{\text{mmHg}}$
pH_A = 7.4	$Z_{CF} = 0.015 \frac{\text{ml/min}}{\text{mmHg}}$	$C_{FB} = 0.209 \frac{\text{ml.}}{\text{mmHg}}$
$c_A^2 = c_F^2 \frac{\text{mEq.}}{\text{liter}}$	$Z_{CB} = 0.0001 \frac{\text{ml/min}}{\text{mmHg}}$	$C_{FS} = 0.049 \frac{\text{ml.}}{\text{mmHg}}$
pH_C = 7.35	$Z_{FR} = 0.075 \frac{\text{ml/min}}{\text{mmHg}}$	$C_{BV} = 0.375 \frac{\text{ml.}}{\text{mmHg}}$
pH_F = 7.3	pH_B = 7.04	

Table 1: (Continued)

Physical and chemical parameters

$\alpha^1 = 0.31 * 10^{-4} \frac{\text{mol.}}{\text{liter mmHg}}$	$\kappa = 10^{-6.10} \frac{\text{moles}}{\text{liter}}$
$\kappa_f = 0.131$ 1/sec.	$\kappa_R = 1.76 * 10^{-5} \frac{\text{liter}}{\text{mole sec.}}$

Buffering parameters

$\beta_C = -16 \frac{\text{mM}}{\text{L pH unit}}$	$B_{CA} = 2.07 \frac{\text{mM}}{\text{L pH unit}}$
$\beta_F \cong \beta_c$	$B_{FC} = B_{CA}$
$\beta_B \cong \beta_c$	$B_{BF} = B_{CA}$

Diffusion parameters

$\mathcal{D}^1_{BC} \equiv K^1 = \frac{0.9 * 3.4}{\alpha^1 \pi^1_{BC}} \frac{\text{liter}}{\text{min.}}$	$\mathcal{D}^2_{BC} \equiv K^2 = K^1 \frac{\text{liter}}{\text{min.}}$	$\mathcal{D}^3_{BC} \equiv K^3 = K^1 \frac{\text{liter}}{\text{min.}}$
$\gamma^1_{BC} = 0.074$	$\gamma^2_{FC} = \gamma^1_{BC}$	$\gamma^3_{BF} = \gamma^1_{BC}$
$\delta^1_{BC} = 0.93$	$\delta^2_{FC} = \delta^1_{BC}$	$\delta^3_{BF} = \delta^1_{BC}$

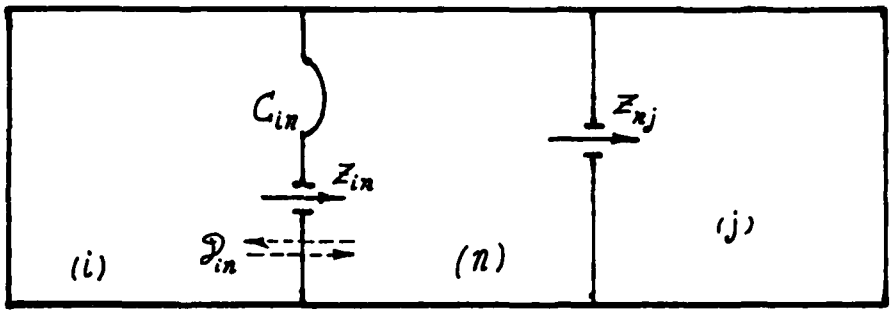

Figure 1:

Three compartments with flow through common boundaries with conductances Z (⊣↑⊢), compliances C (⌒), and transport $\mathcal{D}$ (⇄) coefficients.

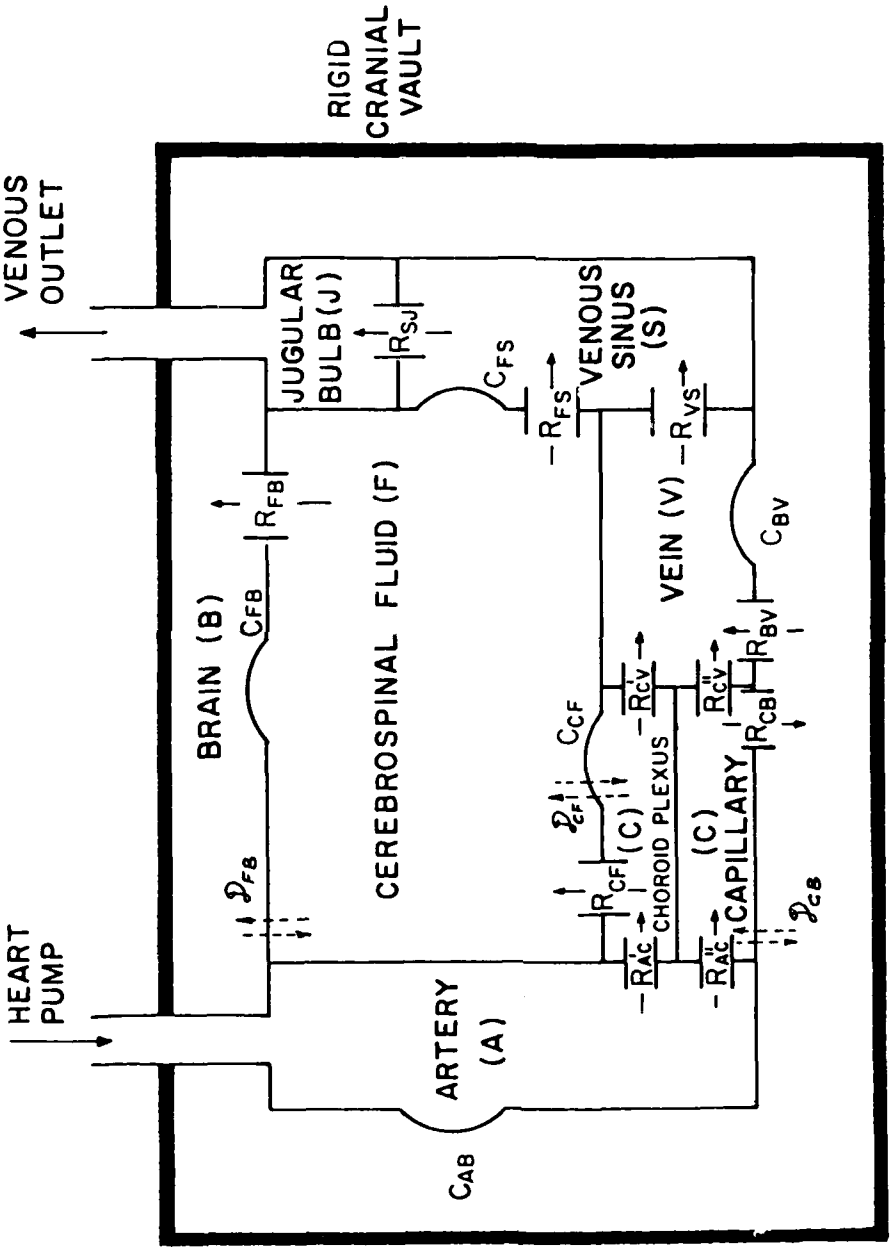

Figure 2:

Cerebral seven compartmental system for perfusion pressure and transport processes.

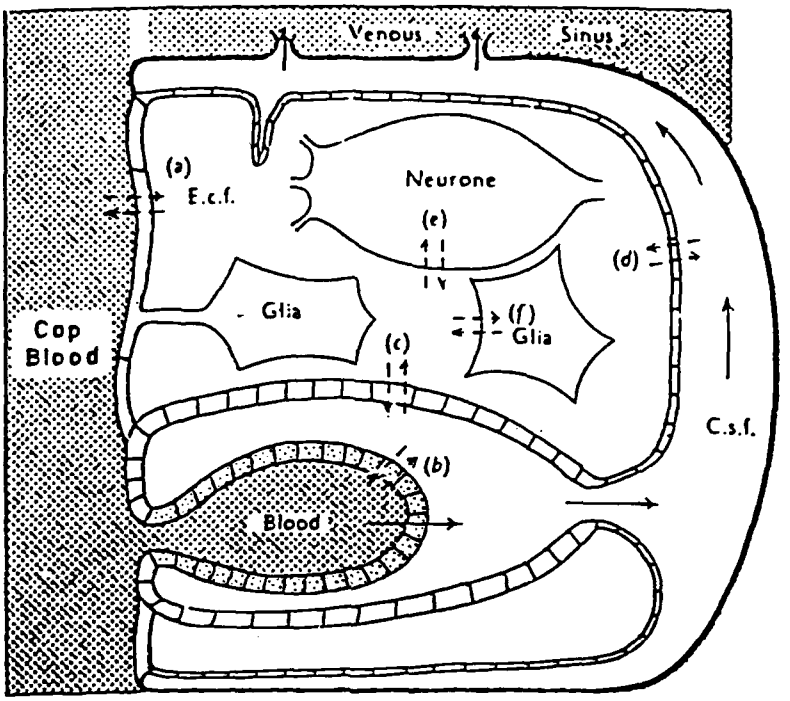

Figure 3:

Schematic of the brain model compartments showing both fluid flow (solid arrows) and diffusion (broken arrows) between compartments. Transport is (a) between extracellular fluid (ECF) and capillary blood, (b) between the capillary blood and cerebrospinal fluid (CSF), (c,d) between the CSF and ECF, (e,f) between the cells (glia and neurons) and the ECF (modified from Davson, 1967 and after Greenberg et al. 1978).

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